

EXPERT
REVIEWS

Prediction of hypersensitivity to antibiotics: what factors need to be considered?

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This review focuses on the epidemiology and different risk factors related to the development of hypersensitivity reactions to antibiotics, with a focus on betalactams and fluoroquinolones, the compounds most frequently involved in these reactions, due to their high level of consumption. The true prevalence of allergic drug reactions is unknown and the corresponding morbidity, mortality and associated economic costs are often underestimated. It is reported that multiple risk factors, related to both the drug and the patient, can modify the clinical expression of immune-mediated drug reactions. These include the chemical properties, molecular weight and administration route of the drug and the age, gender, concomitant diseases and genetic factors of the patient.

KEYWORDS: allergic reactions • antibiotics • drug related • patient related • risk factors

Adverse drug reactions (ADRs) have been defined by the WHO as “any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis or treatment” [1]. ADRs account for 3–6% of all hospital admissions and occur in 10–15% of hospitalized patients. They can be classified according to clinical, pharmacological and chemical characteristics [2]. The pharmacological classification proposed by Rawlins and Thompson [3] is the most widely used, and include two types: predictable (type A) and unpredictable (type B) reactions. Type A reactions represent around 80% of all ADRs; they are related to the pharmacological action of the drug and are dose-dependent. This group includes reactions due to overdose, toxicity, side effects and interactions with others drugs. Type B reactions are generated by mechanisms unrelated to the pharmacological action of the drug, independent of the dose administered and represent 10–15% of the total ADRs. Type B reactions include drug intolerance, idiosyncratic reactions, pseudoallergic reactions and ADRs with an immunological basis (ADRIbs), also known as allergic reactions [4]. They account for 6–10% of all ADRs.

According to the new World Allergy Organisation (WAO) nomenclature, the term drug allergy should remain restricted to those cases with a proven immunological mechanism [4].

Allergic reactions can be further classified according to the Gell and Coombs classification system (TABLE 1) [5] into immediate-type hypersensitivity reactions (mediated by drug-specific IgE antibodies), cytolytic or cytotoxic reactions and immune complex reactions (both of which are mediated by drug-specific IgG or IgM antibodies), and delayed-type hypersensitivity reactions (mediated by drug-specific T lymphocytes). The most common group of drugs that cause these reactions is antibiotics, particularly betalactams (BLs) [6].

This review will focus on different aspects related to the development of hypersensitivity to antibiotics. The epidemiology and risk factors related to BL (TABLES 2 & 3) and fluoroquinolone (FQ) (TABLE 4) antibiotics will be discussed in greater details, since they are the drugs most frequently involved in these reactions. Nowadays, there are no clear risk factors related to the development of drug hypersensitivity reactions that could help to predict them. In this review, we summarize different aspects that may be associated with the occurrence of drug allergic reactions.

Epidemiology

Incidence & prevalence

In spite of many articles dealing with this issue, the true prevalence of allergic drug

Table 1. Gell and Coombs classification of hypersensitivity reactions to drugs.

Type of reaction (mechanisms)	Clinical symptoms
Type 1 or immediate reaction (IgE-mediated)	Urticaria Angioedema Anaphylaxis Anaphylactic shock Bronchial asthma Rhinitis
Type 2 or cytotoxic reaction (antibody-mediated)	Immune hemolytic anemia Thrombocytopenia Blood diseases Organ-specific reaction
Type 3 or immunocomplex reaction (immunocomplex-mediated)	Serum sickness-like syndrome Vasculitis Organ-specific reaction
Type 4 or delayed reaction (T-cell-mediated)	Maculopapular exanthema Delayed urticaria Stevens–Johnson syndrome Toxic epidermal necrolysis Organ-specific reactions Acute generalized exanthematic pustulosis DRESS/DHIS Fixed drug eruption Contact eczema

reactions is not well known, and the associated morbidity, mortality and economic costs are often underestimated [7]. Some systematic studies describe the prevalence and incidence of allergic drug reactions in the general population by using data taken from hospitalized patients and emergency units. From these studies it has been deduced that allergic drug reactions represent between 6 and 10% of all ADRs, however these percentages can vary depending on the methods used to confirm the diagnosis [8]. Little data exist on the true frequency of moderate reactions, which often go unreported.

Drugs involved

The prevalence of allergic reactions to a given drug in a population varies according its level of consumption. Doña *et al.* [6] observed that during the years 2005–2010, the frequency of allergic reactions to BL antibiotics showed the same trend as described in the 80s [9]: with a progressive decrease in the reactions produced by benzylpenicillin (BP) and an increase in the reactions induced by amoxicillin (AX). Importantly, there has been a significant increase in the number of urticaria and anaphylaxis reactions induced by the new BL formula, consisting of a combination of amoxicillin and clavulanic acid (AX-CLV), the consumption of which has increased greatly in the last few years [6,10]. An increase in the number of adverse reactions induced by other non-BL antibiotics such as the quinolones has also been observed [6,11]. Moreover, there has been a decrease in the number of allergic reactions associated with the

sulfonamides and an increase in the reactions produced by other compounds such as the iodinated contrast media [6].

Differences between adults & children

In general, there is much less information about the ADR incidence in the pediatric population. Studies have estimated an incidence of 10.9% for hospitalized children and 1.5% for outpatient children, with a rate of hospital admission due to ADRs of 2.1% [12]. Some studies have shown that the rates of ADRs/drug allergy among children and adolescents are overestimated [13], because many reactions are not subsequently confirmed. In fact, drug hypersensitivity in children is 1.5-times less likely to be confirmed than in adults, and it is particularly lower in those with maculopapular exanthema [14].

In terms of the drugs involved, in a 10-year retrospective cohort study of pediatric patients who experienced an ADR at a community-based, tertiary care children's hospital in the USA [15], antibiotics were identified as the most common cause of ADRs, followed by narcotic analgesics and anticonvulsants. BLs are the most frequently prescribed drugs for children and hypersensitivity is often reported by parents and pediatricians, though confirmation after an allergological work-up varies from 7 to 60% of cases [16,17]. This wide range may be due to the mechanism involved, as the possibility of confirming BL hypersensitivity is higher for patients with IgE-mediated reactions than for those with T-cell-dependent reactions, such as maculopapular exanthema, since it can be hard to distinguish T-cell-mediated reactions from viral infections [14,16,17]; in this sense, a differential diagnosis including serological viral studies and the analysis of the specificity to the culprit drug by patch test, lymphocyte transformation test or ELISPOT should be included, although the drug provocation test may be the confirming diagnostic test.

From all BLs involved in allergic reactions, AX and to a lesser extent cephalosporins are currently the BLs most frequently involved in ADRs among children [16,17]. However, this can be subject to change, as happens in adults [10], with selective reactions to CLV reported also in children [16,18]. These variations in the BLs involved in allergic reactions are thus a reflection of the changes in their pattern of prescription and consumption [6,9]. In a recent study evaluating children with hypersensitivity reactions to BLs, it was shown that although BLs were the drug most frequently involved, only 8% of the children were finally confirmed as allergic [ZAMBONINO MA, CORZO JL, MUÑOZ C *ET AL.* ALLERGY: DIAGNOSTIC EVALUATION OF HYPERSENSITIVITY REACTIONS TO BETA-LACTAM ANTIBIOTICS IN A LARGE POPULATION OF CHILDREN (2013), SUBMITTED].

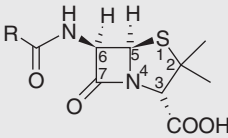
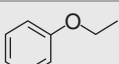
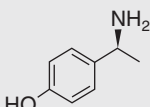
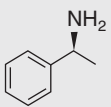
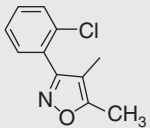
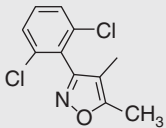
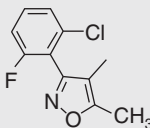
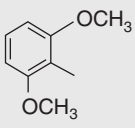
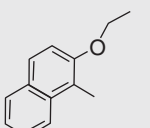
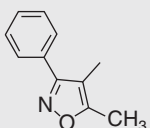
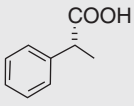
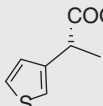
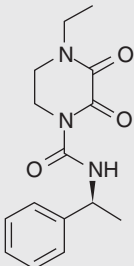
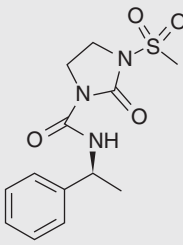
Risk factors in drug allergy reactions

Several risk factors have been shown to modify the clinical expression of immunological drug reactions. These can be related to the drug or the patient.

Drug-related risk factors

Molecular weight & chemical properties
Immunogenicity may be related to molecular weight and structural complexity [19]. However, most of the compounds

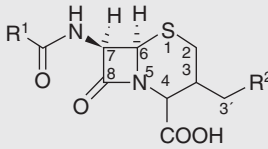
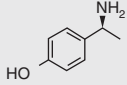
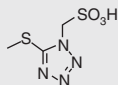
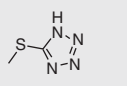
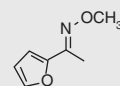
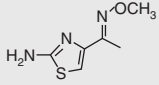
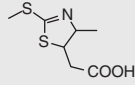
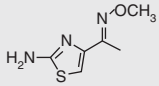
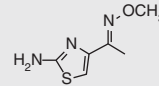
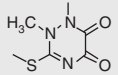
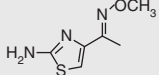
Table 2. Classification and chemicals structures of the most frequently used penicillins.

Penicillins 				
Penicillin type	R	Compound	R	Compound
Natural penicillins		Penicillin G or benzylpenicillin		Penicillin V
Semisynthetic penicillins	Aminopenicillins			
		Amoxicillin		Ampicillin
	Penicillinase-resistant			
		Cloxacillin		Dicloxacillin
		Flucloxacillin		Methicillin
		Nafcillin		Oxacillin
	Carboxypenicillins			
		Carbenicillin		Ticarcillin
	Acylaminopenicillins			
		Piperacillin		Mezlocillin

involved in ADRs have a molecular weight lower than 1000 Da and must bind to macromolecular structures in order to interact with the immune system, according to the hapten hypothesis [20]. Important efforts have been devoted toward the understanding of the pathogenic role of protein haptation by drugs (mainly by BL antibiotics), the identification of adducts formed and their ability to activate the

immune system. Because human serum albumin (HSA) is the most abundant protein in serum, most works have attempted the characterization of HSA adducts with different drugs, such as BP, AX, flucloxacillin and piperacillin, formed either *in vitro* or in the serum of patients [21–23]. Various studies have shown that not only HSA, but also other plasma or cellular proteins participate in the allergic reactions [24,25];

Table 3. Classification and chemicals structures of the most frequently used cephalosporins.

Cephalosporins						
						
Generation	R ¹	R ²	Compound	R ¹	R ²	Compound
First		—H	Cefadroxil			Cephalotin
		—H	Cefalexin			Cefprozil
Second		—CL (3')	Cefaclor			Cefonocid
			Cefamandole			Cefuroxime
Third			Cefodizime		—H	Ceftizoxime
			Cefotaxime			Ceftriaxone
Fourth			Cefepime			

moreover, adducts formed by drugs with different structures may display different stability in biological systems [26]. In addition, databases can be searched to find information on drug targets or biomarkers of different processes [27], to predict proteins with affinity for various drugs or to predict drug toxicity and sensitization risks [28].

The chemical reactivity of drugs and drug metabolites determines their capacity for binding to carrier macromolecules. However, many drugs only become reactive during their metabolism process [29,30]. Although this process is normally associated with a decreased toxicity, metabolites are sometimes more toxic and reactive than the parent drug, and can induce hypersensitivity reactions as have been demonstrated for sulfonamides [31,32], antiepileptic drug [33] and acetaminophen [34]. Reactive metabolites may also arise by mechanisms involving oxidation or photoactivation. This happens in some non-steroidal anti-inflammatory drugs (NSAIDs) such as ketoprofen, antibiotics such as FQs and platelet aggregation inhibitors such as triflusal [35].

The pharmacological interaction concept (p-i concept) [36] proposes that the steric configuration and capacity to react with T-cell receptors can be the factors that confer the ability to activate the immune system.

Mode of administration & dosage

It has been suggested that intermittent and repeated administrations can be more sensitizing than an uninterrupted treatment. Concerning the effects of dosage, it is well known that higher drug concentrations are required for eliciting T-cell responses, compared with IgE-mediated reactions [37,38].

Drug administration route

Drugs administered by a topical, intramuscular or intravenous route are more likely to induce an ADR than those administered orally. In the case of topical administration, this is due to the efficiency of skin penetration; for intravenous and intramuscular administration it is because a high concentration of circulating drugs is reached quickly.

Contaminating & excipient substances

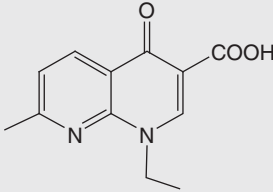
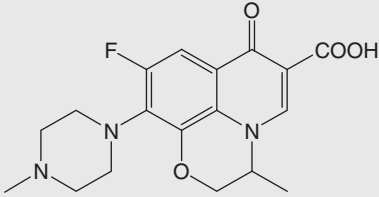
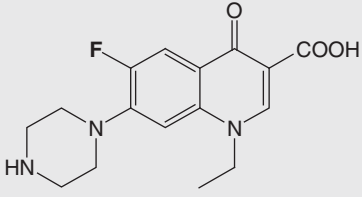
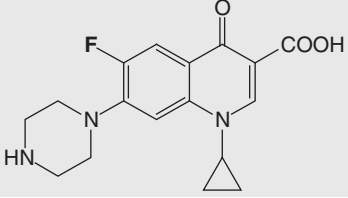
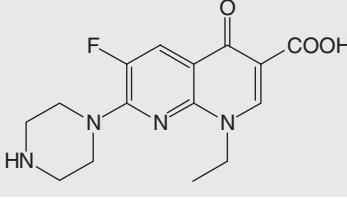
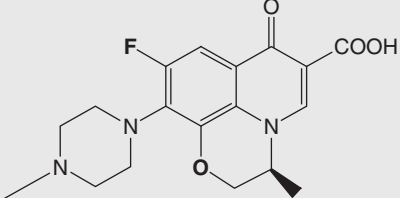
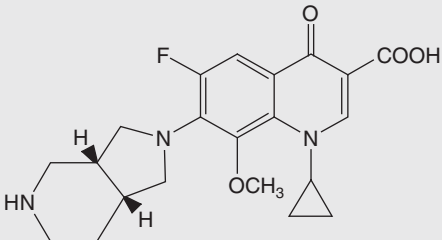
Trace macromolecular contaminants and excipients that facilitate drug solubility may also have a role in acute drug allergy [39].

Patient-related risk factors

Age

Most drug allergic reactions are induced in 20- to 50-year-old patients [12,40]. In general, allergic drug reactions are less

Table 4. Classification and chemicals structures of the most frequently used quinolones.

Generation	Chemical structure	Compound	Chemical structure	Compound
First		Nalidixic acid		
Second		Ofloxacin		Norfloxacin
		Ciprofloxacin		Enoxacin
Third		Levofloxacin		
Fourth		Moxifloxacin		

frequent during childhood due to several factors that include the immaturity of the immune system, a less frequent exposure to drugs and the administration of doses lower than those used in adults [41]. On the other hand, allergic drug reactions are less frequent in subjects older than 65 years than in younger adults, in spite of higher drug consumption. This could be related to the immunosenescence process of aging that is characterized by lymphocyte changes that render the immune system less reactive [42]. Moreover, clinical manifestations of drug allergy in elderly hospitalized patients appear to be similar to those of the non-elderly, however severe reactions are less common [43].

Gender

There are also differences depending on the gender of the subjects with females being more susceptible to develop an allergic

drug reaction than males. Several epidemiological studies have shown 65–70% of subjects who suffer an allergic drug reaction to be female [7,44]. However, no significant differences have been found in the clinical manifestations and mortality between genders [45].

Prior history of allergic reactions to the same drugs or cross-reactive drugs

In some patients, a history of allergic reactions to unrelated drugs also carries an increased risk, especially for IgE-dependent reactions.

Atopy

The prevalence of atopic diseases (eczema, rhinitis and asthma) is increasing worldwide [46] and although atopy has not been generally regarded as a risk factor for most hypersensitivity

drug reactions [47], this position is now being reconsidered. In fact, it has been speculated that exposure to haptens may have contributed to this increase, leading to the so-called hapten-atopy hypothesis [48]. Supporting this connection, it has been recently reported that atopic diseases are associated risk factors for immediate reactions to BLs [49], as well as biological and genetic determinants of atopy [50]. On the other hand, the association between cross-intolerance to NSAIDs and an allergen sensitization, mainly to house dust mites is well known [51]. In a recent study from our group, which included the largest series of patients with hypersensitivity reactions to NSAIDs studied to date, atopy was found in 60% of cases with cross-intolerance, compared with a lower percentage in healthy controls [52].

Concomitant diseases

It has been observed that some concomitant diseases may predispose a patient to the development of an allergic drug reaction. This observation has been described in patients suffering from viral infections such as infections caused by herpesvirus 6 [53,54], Epstein-Barr virus [54], cytomegalovirus [54] and human immunodeficiency virus [55], as well as for other diseases such as asthma [56] and systemic erythematosus lupus [57]. Moreover, it has been observed that certain viral infections can induce an increase in the duration and severity of the symptoms of some clinical entities [58,59].

Genetic factors

Recent years have seen an increase in the study of the genetic factors in drug allergy, made possible by improvements in the available technology. Studies have shown an association between severe hypersensitivity reactions and some haplotypes of the HLA in different ethnic and geographical populations. There is an important variability in the association between ethnic groups, which considers relation between HLA-B*1502 and HLA-B*5801 alleles and the risk of developing severe ADRs to antiepileptic drugs (such as carbamazepine) or allopurinol [60–62]. However, the relation between HLA-B*5701 and abacavir-induced allergic reactions is observed worldwide independent of the ethnic group [63,64]. Unfortunately, no such risk factor has been found for antibiotic adverse reactions. Apart from HLA associations with severe drug allergies, other genetic associations have also been reported such as IL-4, IL-13 and IL-4R [65–68] and a family predisposition to develop allergic reactions has also been described [69].

Betalactam allergy

BL antibiotics are the largest family of antimicrobials. They include a great number of chemical compounds (natural and semisynthetic) and are characterized by the presence of a BL ring in their chemical structure. They have a slow bactericide action, independent of the plasma drug concentration, a low toxicity for humans and a broad spectrum of action, which has been increasing through the years due to the incorporation of new molecules. These attributes have led to BLs being currently

the most widely used antimicrobial in clinical practice, both in primary attention and hospital centers.

Incidence

The prevalence and incidence of allergic reactions to BL antibiotics in the general population is not fully known. Prevalence varies between different studies, with results overestimated when patients are diagnosed using medical history only, and underestimated when patients with allergic reactions are not referred to specialized centers. Epidemiology studies carried out in large series of patients with cutaneous symptoms have shown that only 19% of cases were finally confirmed as having an immediate allergic reaction to BLs [7]. Recently, in a study by Doña *et al.*, it was reported that the immediate allergic reactions to BLs represented 16.07% of all drug hypersensitivity reactions and were responsible for 2.6% of delayed T-cell-mediated reactions mainly maculopapular exanthema [6].

Risk factors

Drug-related risk factors

BLs are intrinsically reactive haptens that bind spontaneously to carrier proteins generating immunogenic adducts [70,71].

The prescription habits of BLs are subjected to changes that influence the frequency of the allergic reactions to these drugs. Thus, AX is nowadays the most frequent drug implicated in allergic reactions to BLs because of its very high consumption [6,9]. In recent years, the consumption changes toward the combination AX-CLV have led to an increase in the prevalence of allergic reactions to CLV [10].

Patient-related risk factors

Females have been shown to have higher rates of ADRs, and the association between female sex and penicillin allergy has been reported in a study carried out by Park *et al.* [72]. In this study, 1921 patients with a history of penicillin allergy were evaluated and it was observed that 83% of the patients with positive penicillin skin test were females.

Several studies have shown the importance of the IgE-mediated pathway in BL allergy, with the involvement of IL-4, IL-13 and the IL-4 receptor- α chain [73]. By focusing on these mechanisms, a number of genetic associations with allergic reaction to BL antibiotics have been shown. These include the E237G variant of Fc ϵ R1 β (high affinity IgE receptor β chain) gene, IL-4R α Q576R polymorphism and IL-4-IL-13-SNP polymorphisms in Chinese populations [65,67], IL-13 (R130Q and -1055C > T variants) and IL-4RA (150V, S478P and Q551R variants) polymorphisms in Italian population [66], and Ile75Val variant of IL-4R α gene two linked IL-10 promoter gene polymorphisms (-819C > T and -592C > A) in Caucasians [68]. A further study in an Italian population reported a higher frequency of HLA-A2 and DRw52, as well as a lower prevalence of DR4 in patients with delayed hypersensitivity reactions to BLs [74].

Fluoroquinolones allergy

The consumption of FQs has increased over the years, in particular for derivatives like ciprofloxacin, levofloxacin and more recently moxifloxacin [75–77]. FQs can induce hypersensitivity reactions through several mechanisms, mostly IgE and T-cell-dependent reactions, with most hypersensitivity reactions being of the IgE type, such as urticaria and anaphylaxis [75–77].

Incidence

In parallel with the increase in consumption, the frequency of hypersensitivity reactions to these drugs has grown in the last decade, and they are becoming the most frequent non-BL antibiotics involved in allergic drug reactions [6,75,76,78]. A German study has shown that the total number of cases of anaphylaxis induced by FQs has increased since 2000 [75]. Similar results have been shown in Spain where the number of hypersensitivity reactions due to FQs rose from 0.54 to 6.85% [6]. T-cell-dependent reactions like maculopapular exanthema, fixed drug eruptions, acute generalized exanthematic pustulosis, Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported less frequently [11].

Risk factors

Drug-related risk factors

Interestingly, the increase in FQ anaphylaxis reported in Germany was mainly related to the introduction of moxifloxacin to the market, with it being involved in 54% of cases, followed by levofloxacin (15%), ciprofloxacin (13%) and ofloxacin (10%) [75]. These results are supported by recent studies carried out in Spain on a large group of patients with IgE reactions to FQs, where moxifloxacin was involved in 63.2% of cases, followed by ciprofloxacin in 28.9% and levofloxacin in 7.9% [76]. Moreover, reactions induced by moxifloxacin were more severe, with 75% of reactions comprising anaphylaxis or anaphylactic shock, versus 54% in those induced by ciprofloxacin [76]. A multivariate analysis showed that one factor associated with the development of hypersensitivity reactions to FQs was the presence of reactions induced by moxifloxacin (odds ratio [OR]: 3.091; 95% CI: 1.160–8.239; adj OR: 13.610; 95% CI: 2.419–76.565) [79]. Reasons for this have not been identified, although it is tempting to speculate that differences in FQ chemical structure may induce metabolites that may differentially react with proteins forming covalent hapten–protein conjugates capable of interacting with the immune system [30]. In fact, the amino-heterocyclic moieties at C-7 appear to be the major target for biotransformation, and for example the diazabicyclic ring at C-7 in moxifloxacin is more reactive than piperazine or a methyl-modified piperazine moiety at C-7 in ciprofloxacin and levofloxacin, respectively [79].

Patient-related risk factors

We have recently evaluated whether certain host conditions such as gender, age, a previous confirmed allergy to BLs or to other drugs were factors contributing to the development of hypersensitivity to FQs and moreover the frequency of different types of

reactions, the time interval between the reaction and the study and the type of symptoms [79]. We found that patients were more likely to be confirmed as having a hypersensitivity reaction when anaphylaxis was the clinical entity, the reaction appeared within 1 h after the drug administration and when the patient had previous hypersensitivity to BLs. In the multivariate analysis immediate reactions (< 1 h) (OR: 52.493; 95% CI: 6.621–416.200; $p = 0.001$) were the most prevalent reactions and only previous hypersensitivity reactions to BLs (OR: 23.654; 95% CI: 1.529–365.853; $p = 0.024$) were identified as risk factor.

The association between allergy to BLs and other antibiotics was described more than 20 years ago and termed multiple drug allergy syndrome. It was found that 21% of allergic patients to penicillins later developed allergy to non-BL antibiotics compared with just 1% of those non-allergic patients [80]. Reasons for that could be an increase of FQ prescription in those allergic patients to BLs or a genetic predisposition. However, no association between FQ allergy and other drugs such as NSAIDs has been detected.

Expert commentary

ADRIbs account for 6–10% of ADRs and this number is growing due to increased prescriptions and the introduction of new compounds. Classical approaches for their diagnosis consist of *in vivo* and/or *in vitro* tests, depending on the immunological mechanisms involved. Because these tests do not have optimal sensitivity, controlled drug administration test has been extensively developed in the last years, for assessing drugs tolerance and to confirm/exclude many drug allergies. Further procedures need to be performed, particularly for the evaluation of those drug hypersensitivity reactions where skin testing is of no value such as quinolone immediate reactions. In this particular case, the basophil activation test has shown to be a useful complementary alternative. Furthermore, novel drug prototypes have been developed in order to include them in the *in vitro* diagnosis of hypersensitivity reactions, particularly those mediated by specific IgE antibodies. Pharmacogenetic studies are now being considered for identifying genetic factors that are predictive of drug allergy. Although they have been useful for non-antibiotic drugs, the results of a number of ongoing studies will be required to determine if genetic markers can be identified that predict the risk for developing ADRIbs to BLs and quinolones.

New antibiotics from the BL group, such as CLV, are gaining importance in the induction of hypersensitivity drug reactions, particularly for immediate reactions, and there is now evidence that they are IgE mediated. With regard to the quinolones, moxifloxacin has emerged as one of the most important drugs in this group for inducing hypersensitivity reactions.

As ADRIbs to antibiotics will continue to appear in the future, further efforts are required for their diagnosis. Reactions can be either specific to any of the drugs in these groups or to several drugs (cross-reactivity), therefore a precise diagnosis is required in order to ensure that the correct culprit drug is detected and thus the ADRIb can be managed appropriately.

Five-year view

Within hypersensitivity reactions to antibiotics, BLs and quinolones will continue to be the most relevant groups of drugs involved. For BLs, AX will be the drug most frequently responsible worldwide, with a high tendency for inducing side chain specific reactions. Because of its low usage, BP allergy will continue to decrease while CLV will increase. Diagnostic methods, both *in vivo* and *in vitro*, will be developed with the aim of determining whether hypersensitivity reactions to BLs are selective for one drug only or caused by several chemically related compounds. Similarly, for quinolones, it is expected that in the

next few years, novel *in vitro* prototype tests will be available for the diagnosis of hypersensitivity reactions.

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Key issues

- Multiple risk factors have been shown to modify the clinical expression of immunologic drug reactions. These factors can be related with the drug or with the subject.
- Drug-related risk factors are: molecular weight and chemical properties, mode and route of administration, contaminating and excipient substances.
- Host-related risk factors are: age, gender, prior history of allergic reactions, atopy, concomitant diseases, genetic factors.
- Beta-lactams (BLs) are the antibiotics most frequently involved in immunologic drug reactions. The consumption changes toward the combination amoxicillin and clavulanic acid (AX-CLV) has led to an increase in the prevalence of allergic reactions to CLV.
- Hypersensitivity to fluoroquinolone (FQ) antibiotics have shown an important increase mainly related with their very high consumption.
- Several studies have shown an association between female sex and penicillin allergy and a number of genetic associations with immediate allergic reaction to BL antibiotics related with IL-4, IL-13 and the IL-4 receptor- α chain gene.
- Patients who had previous hypersensitivity to BLs are more likely to be confirmed as having immediate hypersensitivity to FQs.

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