

Using β -lactam antibiotics in patients with a history of β -lactam allergy: current concepts

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ABSTRACT

β -lactams are the most widely used antibiotic family, but they are also the most common cause of drug-induced hypersensitivity reactions. The estimated prevalence of reported penicillin allergy ranges between 9% and 12%, although a high percentage of patients with a history of penicillin allergy have no subsequent reactions on reexposure to β -lactams. A self-reported penicillin allergy has been associated with antimicrobial resistance, increased cost, intensive care admission, and death, making it essential to establish an accurate diagnosis. In addition to a thorough clinical history, diagnostic methods include skin tests, in vitro tests, and drug-challenge tests. In this review, the diagnosis and management of patients with self-reported penicillin allergy is discussed, including the recently introduced antimicrobial stewardship strategy.

Introduction β -lactams are the most widely used antibiotic family owing to their high safety profile, broad spectrum of activity, and low costs.¹⁻³ They also remain the most common cause of drug-induced hypersensitivity reactions.⁴ Penicillin allergy is the most commonly reported drug allergy, but its true prevalence in the general population is unknown and is usually overestimated.^{5,6} It is estimated between 9% and 12%,^{7,8} and may be as high as 15% in hospitalized patients.⁹ However, a high percentage of patients with a history of penicillin allergy have no subsequent reactions on reexposure to penicillin or β -lactam antibiotics.^{5,6,10-13} This discrepancy is probably caused by multiple factors, including nonallergic adverse events, as for example cutaneous lesions may be part of the natural history of the disease for which antibiotics were prescribed.¹³

β -lactam allergy has considerable implications for public health. The self-reported penicillin allergy has been associated with antimicrobial resistance, increased cost, intensive care admission, and death.¹⁴ Patients with a reported penicillin allergy are more often treated with fluoroquinolones, clindamycin, vancomycin, glycopeptides, and aminoglycosides. Compared with

nonallergic patients, those wrongly labeled as allergic to penicillin have a longer duration of hospitalization and show increased rates of infections caused by *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus*.^{14,15} Therefore, an accurate and rapid diagnosis is crucial to improve the use of antibiotic therapy, increase patient safety, and reduce health care costs.

Recently, β -lactam skin testing has been proposed as an antibiotic stewardship strategy to exclude immunoglobulin E (IgE)-mediated allergy and promote the use of β -lactam therapy in patients with reported allergy; in the case of the negative results of skin tests, a β -lactam could be administered.¹⁵⁻¹⁷ This recommendation is based on the high negative predictive value of skin tests reported by American studies in which benzylpenicillin and penicillin V were predominantly prescribed.¹⁸ However, more recent European studies reported that between 8.4% and 30.7% of patients with negative results reacted to drug challenge.^{12,13,19-21} This is likely due to the fact that in Europe, especially in southern Europe, prescription and consumption of aminopenicillins, amoxicillin/clavulanic acid (AX-CLV),

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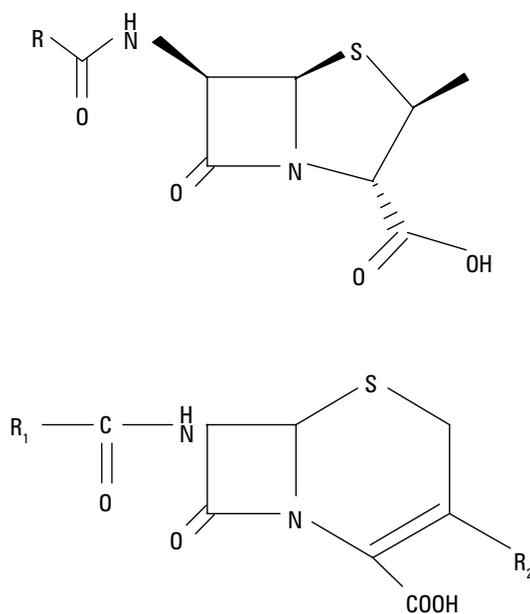
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FIGURE 1 General structure of penicillins and cephalosporins



and cephalosporins is preferred.² As a result, adverse events may occur at a higher rate in European populations if only skin testing is used. Therefore, an adequate allergy evaluation is necessary to exclude β -lactam allergy.^{13,22-24}

β -lactam antibiotics β -lactam antibiotics are a class of broad-spectrum antibiotics with a common chemical characteristic, that is, the presence of a 4-component β -lactam ring. Depending on their chemical structure, β -lactams are grouped into 2 major classes, penicillins and cephalosporins, and 4 minor classes, monobactams, carbapenems, oxacephems, and clavams.

Thus, the basic structure of penicillins consists of this β -lactam ring associated with another thiazolidine ring of 5 components, which gives rise to the nucleus responsible for its biological action, namely, 6-aminopenicillanic acid (6-APA). It has a side chain (R) associated whose variety determines many of the antibacterial and pharmacokinetic characteristics of the different penicillins (FIGURE 1). The cephalosporin nucleus, namely, 7-aminocephalosporanic acid (7-ACA), is analogous to the penicillin nucleus 6-APA. In the case of 7-ACA, the β -lactam ring is fused to a 6-membered dihydrothiazine ring, thus forming the cephem nucleus. Cephalosporins have a side chain in C7 (R1) and different substitutions in C3 (R2) (FIGURE 1). Variations in the chemistry of the C3 side chain affect the drug metabolism, whereas variations in the side chain at C7 alter the resistance to β -lactamases and broaden their antibacterial activity. Carbapenems contain a carbon double bond in place of sulfur in the 5-member thiazolidine ring, while monobactams comprise the β -lactam ring without an attached 5- or 6-membered sulfur ring.²⁵

Antigenic determinants of β -lactams Penicillins and β -lactams are generally considered immunologically haptens and need to bind to carrier molecules to acquire complete immunogenic potency. The binding of the antibiotic to amino groups of autologous proteins induces a conformational modification that causes the immune system to recognize them as strange. The β -lactam rings and the side group are all potentially immunogenic.

Penicillins have been the most studied antibiotics. The β -lactam ring is intrinsically reactive and does not need prior metabolism. The instability of its structure makes it open quickly, allowing the carbonyl groups to form amide-type linkages with the amino groups of the lysine residues of the nearby proteins.²⁶ As approximately 95% of the penicillin molecules are bound to proteins in this manner, the antigenic determinant formed, benzylpenicilloyl (BPO), has been known as the major antigenic determinant of penicillin. BPO has been attached to a weakly immunogenic carrier molecule, called polylysine, to form benzylpenicilloyl polylysine (BPO-PPL), which is used in making skin tests. The remaining part of the penicillin molecule degrades to a range of derivatives which can also act as haptens.²⁷ These are minor determinants accounting for allergic reactions in approximately 10% to 20% of patients.²³ The minor determinant mixture (MDM) has been also used in skin tests.

The progressive increase in the consumption of amoxicillin (AX) has led to an increase in the detection of patients allergic to AX who tolerate benzylpenicillin (BP).²⁸ These reactions are called selective reactions to AX. The major antigenic determinant of AX is the amoxicilloyl amide, which results from the opening of the β -lactam ring by amino groups.²⁹

Although the structure of the possible antigenic elements of cephalosporins is not well known, different experimental studies have proved that they can generate structures able to provoke specific immune response.³⁰ IgE antibodies that react with cephalosporins have been shown to detect a wide range of specificities, although the fundamental antigenic part lies in the side chain R1 and part of the β -lactam ring.³⁰

Finally, considering the great variety of chemical structures susceptible to be formed within the β -lactam antibiotics, the number of hapten-carrier conjugates that can be generated and recognized specifically by the immune system is high.^{29,31-33} Thus, from a clinical point of view, patients can have: 1) selective reactions to a given compound; 2) reactions to different β -lactam sharing an identical side chain, such as AX and cefadroxil; and 3) reactions to the nuclear region of the antibiotic, resulting in a cross-reactivity between different β -lactams.

Allergic reactions to β -lactam antibiotics Drug hypersensitivity or drug allergic reactions have been classified according to distinct criteria. Depending on the immunologic effector mechanism, the

classic work of Coombs and Gell¹ classified reactions into 4 different types (I–IV). Subsequently, some authors have proposed modifications of that classification, such as dividing type II into 2 subtypes² and type IV into 4 subtypes.^{3,4} In addition, the fifth mechanism has been suggested in granulomatous diseases, driven by innate immunity or type 1 or type 2 cytokines.⁵

Clinically, on the basis of the time of appearance of the reaction after drug intake and for diagnostic purposes, hypersensitivity reactions to β -lactams have been classified as immediate or nonimmediate/delayed. Immediate reactions occur within 1 to 6 hours after the last drug administration, whereas nonimmediate reactions may occur any time as from 1 hour after the initial drug administration.^{2,4}

Immediate reactions typically appear within the first hour after the first dose of a new course of treatment. They usually manifest as urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms, or as anaphylaxis or anaphylactic shock. Nonimmediate reactions typically occur after 1 or more days of treatment, with maculopapular exanthemas and delayed urticaria as the most common clinical manifestations. Therefore, regarding allergy to penicillins and other β -lactams, when we attempt to bring those classifications together, different pictures can be found depending on the mechanisms, time interval, dosing, duration of treatment, and clinical presentation (TABLE 1).^{4,34}

Diagnosis of β -lactam allergy In order to reach an adequate diagnosis, a comprehensive medical history is essential, followed by skin tests. *In vitro* tests can be used when available. However, since the medical history is often not reliable and the sensitivity of skin and *in vitro* tests is not optimal, a controlled drug provocation test (DPT) may be required to establish the diagnosis.

The European Network for Drug Allergy has devised various diagnostic algorithms for the evaluation of immediate²³ and nonimmediate reactions.³⁵ Although with limitations, these algorithms, are still useful in the evaluation of patients with a history of allergy to β -lactam antibiotics.

Immediate or immunoglobulin–E-mediated reactions Immediate reactions to β -lactam antibiotics can be assessed by different methods, always starting with a detailed medical history followed by skin tests, determination of specific IgE, or controlled administration of the drug, or any combination thereof (FIGURE 2). Among the available tests, skin tests are considered the most useful technique for establishing a diagnosis of hypersensitivity in immediate reactions. *In vitro* tests have lower sensitivity than skin tests, but in some instances, they can be useful in confirming the diagnosis. However, since the sensitivity of these tests is not optimal, even with a clearly positive history, a controlled administration of

the drug may be required to exclude hypersensitivity in a nonsuggestive history of drug hypersensitivity or to establish a firm diagnosis in the context of a suggestive history with negative or nonconclusive allergy tests.

Medical history A detailed history plays a fundamental role in the evaluation of patients with suspected hypersensitivity to drugs. This is even more important when the exact nature of the structures that trigger the immune reaction is unknown. The medical history allows us to determine whether the reaction was immediate or nonimmediate, according to the latency period between the administration of the antibiotic and the onset of symptoms. In general, anaphylaxis and other immediate reactions like most urticarias or bronchospasms typically develop within minutes after drug administration. Detailed information on the symptoms and their severity should be collected.

Another important parameter that should be obtained from the history is the previous tolerance to the suspected antibiotic or to other β -lactam antibiotics, as well as any later exposure with good tolerance to β -lactam antibiotics, including the eliciting one. This can help us determine the antibiotic that sensitized the patient. In addition, the event of later tolerance to a different β -lactam would suggest a selective reaction. The history should also include other data such as all medications that the patient was taking at the moment of the reaction or the possibility of allergy to other drugs.

However, in many cases, the history can be imprecise because the patients is examined many years after the reaction and they may have lost sensitivity to the antibiotic. Solensky et al³⁶ analyzed different studies and reported that the finding of a positive result in an allergy test in patients with vague or nonsuggestive allergic reactions was not unusual and may have accounted for up to 33% of the cases with positive skin test results. Thus, based solely on the medical history, there might be a percentage of patients with false negative results who should be taken into account and who may react to the antibiotic on new exposure. In a study performed by our group, the medical history as a diagnostic tool showed a sensitivity of 69.8%, specificity of 82.3%, and negative predictive value of 88.7%.³⁷

Skin testing Skin testing has been used for the diagnosis of both immediate and nonimmediate reactions to β -lactam antibiotics. Skin tests have proved to be an important means of predicting which patients are at risk of developing IgE-mediated reactions.^{22,23} Skin tests are generally safe, but systemic reactions may occur, especially in patients with a previous history of anaphylaxis, of whom up to 8% could present an adverse reaction.³⁸ Therefore, testing should be undertaken by professionals with the knowledge, experience,

TABLE 1 Classification of hypersensitivity reactions to β -lactam antibiotics

Type	Common name	Mechanism	Onset of reaction	Clinical characteristics	Characteristics of patients/ applications	Comments
I	Immediate	IgE	Up to 6 h after the last drug administration	Urticaria, angioedema, bronchospasm, rhinitis, conjunctivitis, or anaphylaxis		Can be life-threatening
	Accelerated/immediate	Can be mediated by IgE	Up to 4 days into drug course, but within 1–6 h from last dose	Urticaria/angioedema, and/or wheezing, laryngeal edema		
II	Cytotoxic reactions	IgG lyses the leukocytes, platelets, or red blood cells in the presence of complement		Blood disorders (ie, agranulocytosis, thrombocytopenia, and hemolytic anemia); organ-specific reactions	Patients with prolonged courses of the drug	
III	Immune complex reactions	IgG, IgM, or immune complexes	3–4 weeks after starting treatment	Serum sickness with fever, urticarial rash, arthralgia and lymphadenopathy, vasculitis, organ-specific reactions		
IV	Nonimmediate/delayed reactions	T-cell mediated resulting from the stimulation of distinct T-cell subsets	>3–4 days from the first administration or > 1–2 h from the last administration Onset of rash can occur up to 2–4 weeks after starting or soon after discontinuation of the drug.	Very heterogeneous (generally cutaneous), organ-specific reactions		
IVa	Classic contact-induced hypersensitivity reaction	T cells stimulate IFN- γ -activated macrophages/monocytes		Eczema/dermatitis	Topical use of penicillin; health professional or workers in the manufacturing industry	
IVb		Mediated by Th2 cells producing IL-4 and IL-5 causing in turn IgE release and eosinophil recruitment		Morbiliform or maculopapular rashes; occasionally, DRESS	<ul style="list-style-type: none"> – In up to 10% of patients taking ampicillin and amoxicillin – In up to 70–90% of patients infected with EBV or HPV, who take aminopenicillins – Flare up of DRESS caused by other drugs with amoxicillin – HIV- and CMV-positive patients 	Mild to severe
IVc		CD4 and CD8 cytotoxic T-cell activation producing massive keratinocyte apoptosis particularly in TEN		Bullous exanthemas: SJS and TEN		Can be life-threatening

Abbreviations: CMV, cytomegalovirus; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein–Barr virus; IFN- γ , interferon γ ; HIV, human immunodeficiency virus; HPV, human papillomavirus; Ig, immunoglobulin; IL, interleukin; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; Th2, T-helper 2

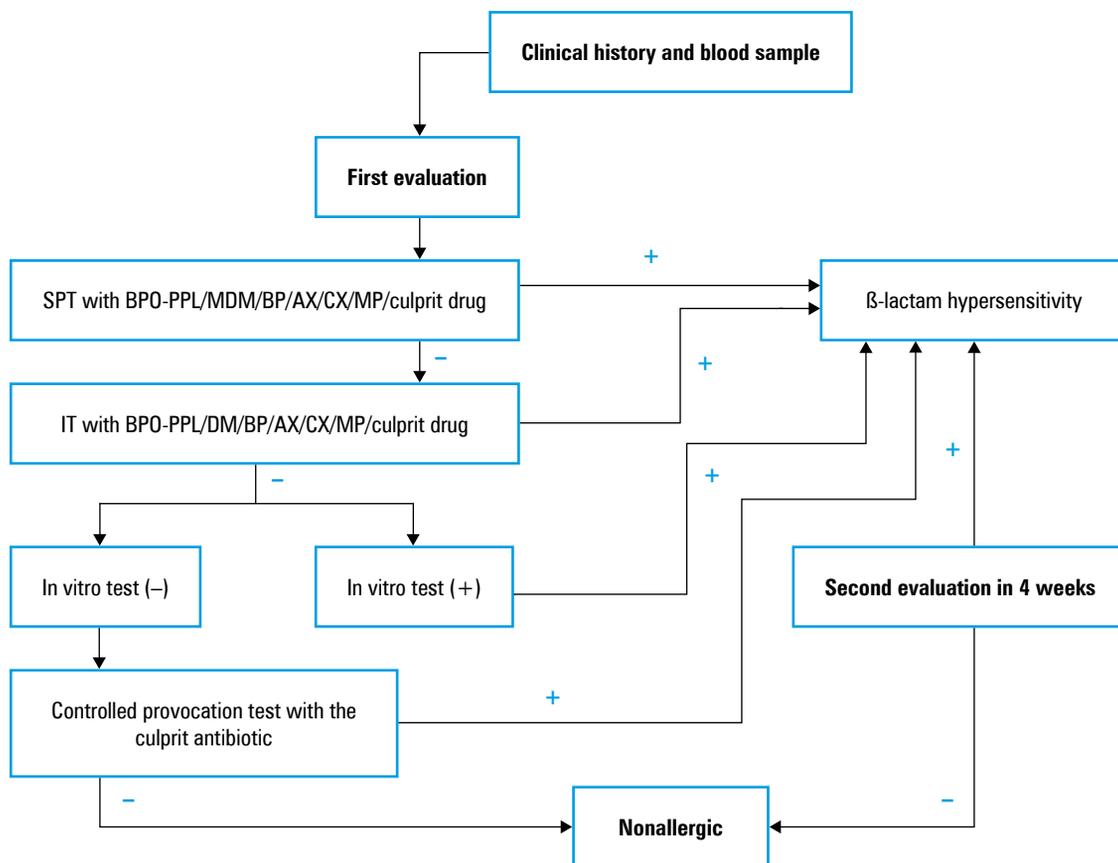


FIGURE 2 Diagnostic algorithm for β -lactam allergy

Abbreviations: AX, amoxicillin; BP, benzylpenicillin; CX, cloxacillin; MDM, minor determinant mixture; IT, intradermal test; MP, meropenem; BPO-PPL, benzylpenicilloyl polylysine; SPT, skin prick test

and training to interpret test results and the ability to manage severe allergic reactions.

Skin tests are usually performed using the skin-prick technique, by pricking the skin with an appropriate needle through an allergen solution. If this does not cause a reaction, an intradermal test can be performed by the injection of 0.02 to 0.05 ml of the drug solution.

In the case of allergy to β -lactams, commercial preparations are available for skin testing, and these have been modified over time. Until 2013, the haptens used were the major determinant of BP, BPO-PPL, and MDM composed of BP, benzylpenicilloate, and benzylpenilloate. At present, BPO is maintained as the major determinant, in this case conjugated to octalpolylysine, and a single minor determinant, benzylpenilloate, not present in the remaining smaller determinants described due to their high instability.³⁹ In addition, Romano et al⁴⁰ reported a small percentage of β -lactam allergic patients (<5%) who tested negative for BPO-PPL and MDM, but positive for BP, recommending the inclusion of BP in the battery of skin tests.

At present, due to the changing patterns of β -lactam use, and the appearance of side-chain-specific reactions, it is necessary to use other determinants, such as AX or some

cephalosporins.^{22,23} The same happens with the use of β -lactamase inhibitors, as in recent years, patients with selective hypersensitivity to clavulanic acid have been reported.⁴¹ Therefore, the study of immediate allergy to β -lactam antibiotics is now more complex owing to the wide panel of β -lactams prescribed today.

The sensitivity and specificity of skin tests are difficult to determine because the diagnostic gold standard, that is, DPT, is not performed in all patients for ethical reasons, given the risks that this procedure entails. In our experience, in patients with a previous life-threatening reaction, a 1/10 to 1/1000 dilution of skin test reactants is recommended.

The percentage of positive skin test results in patients with a clinical history of a β -lactam allergic reaction varies between 7% and 76%, according to different studies.^{10,13,42-45} The higher frequency of positive skin test results is reported in patients with very suggestive histories of immediate reaction, such as urticaria and anaphylaxis, and also when skin tests are made just a short time after the reaction has occurred, because a long interval between the reaction and skin testing reduces the likelihood of a positive response.^{22,46}

BPO-PPL, the major determinant of penicillin, has been historically the most relevant. The first studies reported positive results in more than 70% of patients.^{47,48} The use of the MDM has been also considered important, as some studies suggested that 10% to 20% of patients with penicillin allergy tested positive for these determinants and negative for BPO-PPL.²³ However, since the 1990s, the sensitivity of penicillin skin tests using BPO-PPL and MDM has been progressively declining.²⁸ It is likely due to the decreasing use of parenteral penicillin and the increased use of semisynthetic penicillins, such as aminopenicillins and cephalosporins, leading to an increase in the number of patients with selective side-chain-specific allergic reactions.^{28,49,50}

In the 1990s, the percentage of positive skin test results with AX or ampicillin in patients with penicillin allergy ranged from 26% to 47.5%.^{28,49} In a recently published series, we found that 36% of patients tested positive only for AX.¹³ The description of selective reactions to clavulanic acid has highlighted the need to include this drug in the diagnostic workup.⁴¹

Despite using a large panel of β -lactams, the sensitivity of skin tests is not optimal.^{23,51} In addition, their sensitivity seems to have been decreasing in recent years, with a significant percentage of patients requiring DPTs for diagnosis.²¹ It is also important to emphasize that in immediate reactions to β -lactams, the sensitivity of skin tests decreases over time. Prospective studies have confirmed that skin test reactivity is lost over time in penicillin-allergic patients, with only 30% to 50% of patients with initial positive results remaining positive after 5 years⁴⁶; the percentage of loss is even higher in the case of aminopenicillins.⁴⁶ It is unknown what percentage of patients becomes positive again after a new exposure to a β -lactam, a phenomenon known as re-sensitization. Several studies have indicated that between 1% and 27.9% of patients may be re-sensitized after β -lactam administration.^{11,13,44,52,53} For this reason, in patients with a clear history of an immediate reaction after the administration of a β -lactam derivative, who show negative results in skin and in vitro tests and good tolerance to a DPT, a reevaluation after 1 month is strongly recommended,^{13,23,24} particularly if the reaction occurred more than 1 year earlier.

Drug provocation tests DPTs are based on the controlled administration of increasing doses of the drug to a patient with a history suggestive of drug allergy. This can be either the suspected culprit or an alternative structurally or pharmacologically related drug. Briefly, a DPT is usually performed in a single-blinded procedure in patients with negative skin and in vitro test results. Escalating doses of the drug are typically given at intervals of 30 to 90 minutes until the full therapeutic dose is reached.⁵⁴ If symptoms appear during the DPT, the procedure must be stopped. This procedure is not recommended in patients with a

history of life-threatening reactions.⁵⁴ Moreover, this diagnostic tool can be used to find alternatives to the culprit drug and to assess tolerance to potentially cross-reactive drugs.⁵⁵

Immunoassays IgE-mediated allergy to β -lactams is diagnosed with antibody-based immunoassays that use several solid phases (agarose, cellulose discs), carrier molecules (human serum albumin, polylysine), and different determinants (BP, AX, and cephalosporins). Today, the ImmunoCAP system (Thermo-Fisher, Uppsala, Sweden), which works by a high surface-capacity solid-phase assay using a secondary fluorolabeled antibody, remains the most widely used commercial method for diagnosing β -lactam allergy. The specificity of this method ranges from 83.3% to 100%, and sensitivity—from 12.5% to 25%.⁵⁶

Basophil activation test The basophil activation test has been used as a diagnostic test for IgE-mediated reactions and is based on the quantification of different activation or degranulation markers on the basophil surface after stimulation by the culprit drug.^{57,58} Several studies have analyzed the value of the test in the diagnosis of IgE-mediated reactions to β -lactams. The first studies using the basophil activation test to analyze β -lactam allergy reported a sensitivity of 50% in patients who tested positive for at least 1 penicillin in a skin test and a specificity of 93%.^{59,60} Similar data were obtained in a multicenter study,⁶¹ which reported a sensitivity of 50% and a specificity between 89% and 97%, and emphasized the need to test more than 1 β -lactam at a minimum of 2 concentrations to obtain optimal results.

Nonimmediate reactions The European guidelines^{22,35,62,63} suggest evaluating nonimmediate reactions to β -lactam by both patch tests and intradermal tests with delayed readings. The sensitivity of skin tests in nonimmediate reactions is lower than that of immediate reactions.^{22,35} Patch tests are considered to be safer and to be the first step in the evaluation of severe cutaneous reactions.⁶²

A greater sensitivity for the intradermal test compared with patch tests in diagnosing nonimmediate reactions has been reported.⁶⁴ It has been described that the overall sensitivity of delayed-reading skin tests may have been improved using the combination of intradermal and patch tests.⁶⁵

Drug provocation tests This procedure is important in nonimmediate reactions for which skin tests sensitivity is low.²² However, DPTs should never be performed in patients who have experienced severe reactions such as vasculitis syndromes, exfoliative dermatitis, erythema multiforme major/ Stevens–Johnson syndrome, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms, and toxic epidermal necrolysis.⁵⁴

TABLE 2 Groups of β -lactams sharing an identical R1 side chain

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cephalexin	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephadrine	Cefpodoxime	Cephalotin		
	Cefaclor	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			

Lymphocyte transformation test The lymphocyte transformation test is the most common in vitro test for assessing specific cellular sensitization.^{66,67} It has been used to diagnose β -lactam allergy and has shown variable sensitivity (ranging from 25% to 79%) for a nonimmediate allergic reaction to penicillin.⁶⁶⁻⁶⁸ However, false positive results were reported in nonreactive patients who had been recently exposed to drugs.⁶⁷

Cross-reactivity Cross reactivity between penicillins Cross-reactivity between drugs is due to the existence of antibodies or cells that recognize an identical or similar structure present in different drugs. In clinical practice, it represents the risk of developing allergic reactions to related drugs in patients who had a previous reaction to a single β -lactam.

Regarding penicillins, there are 2 major groups of allergic patients: nonselective and selective responders. Nonselective responders are sensitized to the whole penicillin group because they have IgE antibodies that recognize the common determinants of BP (BPO-PPL and MDM). Selective responders have positive skin test results for semisynthetic penicillins, especially AX, negative skin test results for BP determinants, and tolerate the administration of BP. The frequency of each group has varied over time, as the use of AX has increased. According to different studies, the frequency of selective responders to AX can vary from 40%^{13,28} to almost 80% of patients.⁴¹ It has been reported that up to 22% of patients with AX-CLV-selective reactions are selectively allergic to clavulanic acid and tolerate AX and BP.⁴¹

Cross reactivity between penicillins and cephalosporins There have been numerous studies of cross-reactivity between penicillins and cephalosporins. Most of them were performed in patients allergic to penicillins and evaluated cephalosporin sensitization. Studies published before 1980 found a high degree of cross-reactivity, up to 60%, between BP and first-generation cephalosporins, due to the similarity of the side chain in R1 or perhaps to contamination of the first cephalosporin preparations with traces of penicillin.⁶⁹ Subsequent studies have shown much lower cross-reactivity. These studies have revealed the importance of the similarity of side chains for the degree of cross-reactivity between penicillins and cephalosporins. Thus, anti-BPO antibodies react with cephalosporins having a similar chain in position R1 to that of BP, such

as cephalothin, cefamandole, and cephaloridine (TABLE 2). In contrast, they do not react or scarcely react with cephalosporins whose side chains have a different structure, such as cefuroxime and cefotaxime.⁷⁰

The situation is similar for cross-reactivity to cephalosporins in patients with selective sensitization to aminopenicillins. Cross-reactivity studies performed with the first-, second-, and third-generation cephalosporins carrying different side chains in patients allergic to BP or with selective sensitization to AX have not demonstrated cross-reactivity⁷¹ or a very low frequency (around 3%) of cross-reactivity.⁷² On the contrary, the cross-reactivity of AX with aminocephalosporins which have an identical side chain ranges from 14% to 38% for cefadroxil^{73,74} and around 30% for cephalexin.⁷⁵

However, the lack of complete cross-reactivity indicates that, in addition to the side chain, other structures of the molecule of both β -lactams are important for recognition by IgE antibodies. Thus, in a study of 128 patients allergic to penicillin, 14 had positive skin test results for cephalosporins, and 4 of them had different patterns of reactivity with cephalosporins that could not be explained by the similarity of side chains or by the identity of the β -lactam ring.⁷² For this reason, it may be risky to treat penicillin-allergic patients with cephalosporins based only on the side chain structure, without performing an allergy study first.

With respect to T-cell-mediated delayed hypersensitivity to penicillins, the frequency of positivity in cephalosporin studies ranges from 2.8% to 31%.^{76,77}

Cross-reactivity between cephalosporins Studies of the cross-reactivity between cephalosporins are much less numerous but have shown that cross-reactivity is largely based on the similarity of the R1 side chain chemical structure.²⁹ In contrast, the R2 side chain is unlikely to contribute to the formation of its antigenic determinants and to cross-reactivity because this chain is fragmented and lost during the cephalosporin degradation process.²⁹

Studies have shown that around 50% to 60% of cephalosporin-allergic patients are allergic to a single cephalosporin, while the remaining patients react to several different cephalosporins.^{33,78} In most patients, the reactivity can be explained by the presence of identical R1 side chains, such as ceftriaxone, cefotaxime, and cefepime,

or very similar side chains, such as cefuroxime, ceftazidime, and the 3 cephalosporins mentioned above (TABLE 2).^{33,46,79} However, other studies have shown that the risk of developing a reaction does not depend only on the structural similarities between the side chains; therefore, an allergy test should always be performed before the administration of another cephalosporin.^{80,81}

Cross-reactivity with carbapenems Cross-reactivity between penicillins and carbapenems is rare. Recent cross-reactivity studies have shown a frequency of around 1%, much lower than that in earlier publications.⁸²⁻⁸⁵ In one of the largest series, 212 adults allergic to penicillin showed negative skin test results for imipenem–cilastatin, meropenem, and ertapenem. All patients except one tolerated a carbapenem–challenge test, which showed negative results.⁸⁶ Cross-reactivity between cephalosporins and carbapenems is also low: 1% for meropenem and 2% for imipenem.⁸⁷ In nonimmediate reactions, the reported frequency ranges from 0% to 5% according to different studies.⁸⁸⁻⁹⁰

There have been very few studies evaluating cross-reactivity between different carbapenems. Most publications are isolated cases in which tolerance to a different carbapenem was demonstrated. Noguerado-Mellado et al⁹¹ described 2 patients with delayed hypersensitivity to carbapenems. One of the patients developed a micropapular rash with imipenem. Intradermal skin tests showed positive results for imipenem in delayed reading, but negative for meropenem. In addition, the patient tolerated meropenem. The second patient developed a generalized desquamative rash with mucosal involvement during treatment with meropenem. The intradermal test result was positive for meropenem but negative for imipenem, and the patient tolerated imipenem. The lack of cross-reactivity between imipenem and meropenem in these 2 patients suggests that side chains, which are different, may play an important role in antigen recognition.⁹¹

A case of anaphylactic reaction to imipenem–cilastatin has also been reported, with positive skin test results and specific IgE for imipenem–cilastatin, and negative for meropenem and cilastatin.⁹² No cases of selective sensitization to cilastatin have been reported.

Cross-reactivity with monobactams Patients with immediate or delayed allergy to penicillins usually tolerate the administration of aztreonam.⁸⁶ In a study of 16 patients with cystic fibrosis allergic to semisynthetic penicillins, 1 patient was found to have positive skin test results for aztreonam. However, it cannot be excluded that it could have been cosensitization, since they were patients who had received repeated treatments with aztreonam.⁹³ With regards to cephalosporins, up to 3% of patients have positive skin test results for aztreonam.⁸⁷ A case of cross-reactivity

with ceftazidime has been described, as the R1 side chain is the same in both drugs.⁹⁴

Conclusions β -lactams are antibiotics associated with a higher rate of adverse immune reactions. This fact is associated with a clear overdiagnosis of allergy to β -lactams. The fear of developing severe allergic reactions precludes the use of these antibiotics in patients that would clearly benefit from them, which usually implies lower treatment effectiveness and a higher incidence of adverse reactions. The diagnosis of β -lactam allergy relies on a comprehensive medical history, skin tests, in vitro tests, and, when indicated, DPTs. Nowadays, skin tests and specific IgE have demonstrated to be useful tools in the diagnosis of immediate hypersensitivity reactions to β -lactams. Nevertheless, their sensitivity and specificity are insufficient, and DPTs may be necessary in up to 30% of patients.

In this context, in the setting of presumably allergic patients without a confirmed positive diagnosis urgently requiring a β -lactam antibiotic, the so called antimicrobial stewardship programs are being developed. In the case of β -lactams, these programs are based on skin testing with β -lactam in patients with suspected β -lactam allergic reactions and, if negative, the administration of a full dose of the β -lactam. Although this could be an interesting approach, we believe that the sensitivity and specificity of skin tests with β -lactam are not high enough to use skin tests in this way. Moreover, there is a possibility of developing allergic reactions when performing skin tests and also during the administration of the full dose of the drug. Therefore, we believe that an appropriate allergy study, including a full battery of β -lactam determinants and a controlled challenge by trained staff is safer and has the advantage of providing accurate information about cross-reactivity.

REFERENCES

- 1 Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. *Lancet Infect Dis.* 2010; 10: 167-175.
- 2 Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. *Lancet.* 2001; 357: 1851-1853.
- 3 Wilke MS, Lovering AL, Strynadka NC. Beta-lactam antibiotic resistance: a current structural perspective. *Curr Opin Microbiol.* 2005; 8: 525-533.
- 4 Torres MJ, Blanca M. The complex clinical picture of β -lactam hypersensitivity: penicillins, cephalosporins, monobactams, carbapenems, and clavams. *Med Clin North A.* 2010; 94: 805-820.
- 5 Solensky R. Hypersensitivity reactions to beta-lactam antibiotics. *Clin Rev Allergy Immunol.* 2003; 24: 201-220.
- 6 Kerr JR. Penicillin allergy: a study of incidence as reported by patients. *Br J Clin Pract.* 1994; 48: 5-7.
- 7 Albin S, Agarwal S. Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. *Allergy Asthma Proc.* 2014; 35: 489-494.
- 8 Picard M, Begin P, Bouchard H, et al. Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. *J Allergy Clin Immunol Pract.* 2013; 1: 252-257.
- 9 Lee CE, Zembower TR, Fotis MA, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med.* 2000; 160: 2819-2822.
- 10 Moreno E, Dávila I, Laffond E, et al. Immediate allergic reactions to β -lactams: Diagnostic accuracy of skin tests. *Ann Allergy Asthma Immunol.* 2011; 107: 89-90.

- 11 García Núñez I, Barasona Villarejo MJ, et al. Diagnosis of patients with immediate hypersensitivity to beta-lactams using retest. *J Investig Allergol Clin Immunol*. 2012; 22: 41-47.
- 12 Dona I, Blanca-Lopez N, Torres MJ, et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Investig Allergol Clin Immunol*. 2012; 22: 363-371.
- 13 Moreno E, Laffond E, Munoz-Bellido F, et al. Performance in real life of the European Network on Drug Allergy algorithm in immediate reactions to beta-lactam antibiotics. *Allergy*. 2016; 71: 1787-1790.
- 14 Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy*. 2011; 31: 742-747.
- 15 Blumenthal KG, Shenoy ES, Varughese CA, et al. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. *Ann Allergy Asthma Immunol*. 2015; 115: 294-300 e2.
- 16 Heil EL, Bork JT, Schmalzle SA, et al. Implementation of an infectious disease fellow-managed penicillin allergy skin testing service. *Open Forum Infect Dis*. 2016; 3: ofw155.
- 17 Leis JA, Palmay L, Ho G, et al. Point-of-care beta-lactam allergy skin testing by Antimicrobial Stewardship Programs: A Pragmatic Multicenter Prospective Evaluation. *Clin Infect Dis*. 2017. doi:10.1093/cid/cix512
- 18 Bourke J, Pavlos R, James I, et al. Improving the effectiveness of penicillin allergy de-labeling. *J Allergy Clin Immunol Pract*. 2015; 3: 365-334.
- 19 Messaad D, Sahla H, Benahmed S, et al. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med*. 2004; 140: 1001-1006.
- 20 Audicana Berasategui MT, Barasona Villarejo MJ, Corominas Sanchez M, et al. Potential hypersensitivity due to the food or food additive content of medicinal products in Spain. *J Investig Allergol Clin Immunol*. 2011; 21: 496-506.
- 21 Bousquet PJ, Pipet A, Bousquet Rouanet L, et al. Oral challenges are needed in the diagnosis of β -lactam hypersensitivity. *Clin Exp Allergy*. 2008; 38: 185-190.
- 22 Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy*. 2009; 64: 183-193.
- 23 Torres MJ, Blanca M, Fernandez J, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy*. 2003; 58: 961-972.
- 24 Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy*. 2014; 69: 420-437.
- 25 Asbel LE, Levison ME. Cephalosporins, carbapenems, and monobactams. *Infect Dis Clin North Am*. 2000; 14: 435-447.
- 26 Levine BB. Immunologic mechanisms of penicillin allergy. A haptenic model system for the study of allergic diseases of man. *N Engl J Med*. 1966; 275: 1115-1125.
- 27 Levine BB, Redmond AP. Minor haptenic determinant-specific reagins of penicillin hypersensitivity in man. *Int Arch Allergy Appl Immunol*. 1969; 35: 445-455.
- 28 Torres J, Romano A, Mayorga C, et al. Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy*. 2001; 59: 850-856.
- 29 Ariza A, Mayorga C, Fernandez TD, et al. Hypersensitivity reactions to beta-lactams: relevance of hapten-protein conjugates. *J Investig Allergol Clin Immunol*. 2015; 25: 12-25.
- 30 Perez-Inestrosa E, Suau R, Montanez MI, et al. Cephalosporin chemical reactivity and its immunological implications. *Curr Opin Allergy Clin Immunol*. 2005; 5: 323-330.
- 31 de Haan P, de Jonge AJ, Verbrugge T, et al. Three epitope-specific monoclonal antibodies against the hapten penicillin. *Int Arch Allergy Appl Immunol*. 1985; 76: 42-46.
- 32 Mayorga C, Obispo T, Jimeno L, et al. Epitope mapping of beta-lactam antibiotics with the use of monoclonal antibodies. *Toxicology*. 1995; 97: 225-234.
- 33 Romano A, Mayorga C, Torres MJ, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. *J Allergy Clin Immunol*. 2000; 106: 1177-1183.
- 34 Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy*. 2015; 45: 300-327.
- 35 Romano A, Blanca M, Torres MJ, et al. Diagnosis of nonimmediate reactions to beta-lactam antibiotics. *Allergy*. 2004; 59: 1153-1160.
- 36 Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol*. 2000; 85: 195-199.
- 37 Moreno E. [Usefulness of available diagnostic tests in the evaluation of beta-lactam hypersensitivity reactions. Applicability of an artificial neural network as a diagnostic predictor]. Doctoral Thesis. University of Salamanca, Spain; 2001. Spanish.
- 38 Co Minh HB, Bousquet PJ, Fontaine C, et al. Systemic reactions during skin tests with beta-lactams: a risk factor analysis. *J Allergy Clin Immunol*. 2006; 117: 466-468.
- 39 Fernandez J, Torres MJ, Campos J, et al. Prospective, multicenter clinical trial to validate new products for skin tests in the diagnosis of allergy to penicillin. *J Investig Allergol Clin Immunol*. 2013; 23: 398-408.
- 40 Romano A, Bousquet-Rouanet L, Viola M, et al. Benzylpenicillin skin testing is still important in diagnosing immediate hypersensitivity reactions to penicillins. *Allergy*. 2009; 64: 249-253.
- 41 Blanca-Lopez N, Perez-Alzate D, Ruano F, et al. Selective immediate responders to amoxicillin and clavulanic acid tolerate penicillin derivative administration after confirming the diagnosis. *Allergy*. 2015; 70: 1013-1019.
- 42 Gadde J, Spence M, Wheeler B, et al. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA*. 1993; 270: 2456-2463.
- 43 Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy*. 1988; 18: 515-540.
- 44 Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol*. 2008; 100: 37-43.
- 45 Van Dellen RG, Walsh WE, Peters GA, et al. Differing patterns of wheal and flare skin reactivity in patients allergic to the penicillins. *J Allergy*. 1971; 47: 230-236.
- 46 Blanca M, Torres MJ, García JJ, et al. Natural evolution of skin test sensitivity in patients allergic to β -lactam antibiotics. *J Allergy Clin Immunol*. 1999; 103: 918-924.
- 47 Sullivan TJ, Wedner HJ, Shatz GS, et al. Skin testing to detect penicillin allergy. *J Allergy Clin Immunol*. 1981; 68: 171-180.
- 48 Green GR, Rosenblum AH, Sweet LC. Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. A cooperative prospective study of the penicillin study group of the American Academy of Allergy. *J Allergy Clin Immunol*. 1977; 60: 339-345.
- 49 Blanca M, Vega JM, Garcia J, et al. Allergy to penicillin with good tolerance to other penicillins: study of the incidence in subjects allergic to betalactams. *Clin Exp Allergy*. 1990; 20: 475-481.
- 50 Silviudan F, McPhillips S, Warrington R. The frequency of skin test reactions to side-chain penicillin determinants. *J Allergy Clin Immunol*. 1993; 91: 694-701.
- 51 Torres E, Villanueva R, Bou G. Comparison of different methods of determining beta-lactam susceptibility in clinical strains of *Pseudomonas aeruginosa*. *J Med Microbiol*. 2009; 58: 625-629.
- 52 Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med*. 2002; 8: 822-826.
- 53 Lopez-Serrano MC, Caballero MT, Barranco P, et al. Booster responses in the study of allergic reactions to beta-lactam antibiotics. *J Investig Allergol Clin Immunol*. 1996; 6: 30-35.
- 54 Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy*. 2003; 58: 854-863.
- 55 Kuruvilla M, Khan DA. Anaphylaxis to drugs. *Immunol Allergy Clin North Am*. 2015; 35: 303-319.
- 56 Fontaine C, Mayorga C, Bousquet PJ, et al. Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate β -lactam allergy. *Allergy*. 2007; 62: 47-52.
- 57 Knol EF, Mul FP, Jansen H, et al. Monitoring human basophil activation via CD63 monoclonal antibody 435. *J Allergy Clin Immunol*. 1991; 88: 328-338.
- 58 Mangoldt EA, Van Gasse AL, Bastiaensen A, et al. Flow-assisted basophil activation tests in immediate drug hypersensitivity: two decades of Antwerp experience. *Acta Clin Belg*. 2016; 71: 19-25.
- 59 Torres MJ, Padial A, Mayorga C, et al. The diagnostic interpretation of basophil activation test in immediate allergic reactions to betalactams. *Clin Exp Allergy*. 2004; 34: 1768-1775.
- 60 Sanz ML, Gamboa PM, Antepara I, et al. Flow cytometric basophil activation test by detection of CD63 expression in patients with immediate-type reactions to betalactam antibiotics. *Clin Exp Allergy*. 2002; 32: 277-286.
- 61 De Week AL, Sanz ML, Gamboa PM, et al. Diagnosis of immediate-type beta-lactam allergy in vitro by flow-cytometric basophil activation test and sulfidoleukotriene production: a multicenter study. *J Investig Allergol Clin Immunol*. 2009; 19: 91-109.
- 62 Barbaud A, Goncalo M, Bruynzeel D, et al. European Society of Contact D. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis*. 2001; 45: 321-328.
- 63 Brockow K, Romano A, Blanca M, et al. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy*. 2002; 57: 45-51.
- 64 Torres MJ, Sanchez-Sabate E, Alvarez J, et al. Skin test evaluation in nonimmediate allergic reactions to penicillins. *Allergy*. 2004; 59: 219-224.
- 65 Ponvert C, Perrin Y, Bados-Albiero A, et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol*. 2011; 22: 411-418.
- 66 Nyfeler B, Pichler WJ. The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. *Clin Exp Allergy*. 1997; 27: 175-181.
- 67 Luque I, Leyva L, Jose Torres M, et al. In vitro T-cell responses to beta-lactam drugs in immediate and nonimmediate allergic reactions. *Allergy*. 2001; 56: 611-618.

- 68 Warrington RJ, Tse KS. Lymphocyte transformation studies in drug hypersensitivity. *Can Med Assoc J.* 1979; 120: 1089-1094.
- 69 Madaan A, Li JT. Cephalosporin allergy. *Immunol Allergy Clin North Am.* 2004; 24: 463-476.
- 70 Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: a meta-analysis. *Otolaryngol Head Neck Surg.* 2007; 136: 340-347.
- 71 Novalbos A, Sastre J, Cuesta J, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. *Clin Exp Allergy.* 2001; 31: 438-443.
- 72 Romano A, Gueant-Rodriguez RM, Viola M, et al. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med.* 2004; 141: 16-22.
- 73 Sastre J, Quijano LD, Novalbos A, et al. Clinical cross-reactivity between amoxicillin and cephadroxil in patients allergic to amoxicillin and with good tolerance of penicillin. *Allergy.* 1996; 51: 383-386.
- 74 Miranda A, Blanca M, Vega JM, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. *J Allergy Clin Immunol.* 1996; 98: 671-677.
- 75 Audicana M, Bernaola G, Urrutia I, et al. Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. *Allergy.* 1994; 49: 108-113.
- 76 Trcka J, Seitz CS, Brocker EB, et al. Aminopenicillin-induced exanthema allows treatment with certain cephalosporins or phenoxymethyl penicillin. *J Antimicrob Chemother.* 2007; 60: 107-111.
- 77 Phillips E, Knowles SR, Weber EA, et al. Cephalixin tolerated despite delayed aminopenicillin reactions. *Allergy.* 2001; 56: 790.
- 78 Antunez C, Blanca-Lopez N, Torres MJ, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol.* 2006; 117: 404-410.
- 79 Saenz de San Pedro B, Mayorga C, Torres MJ, et al. Boosted IgE response after anaphylaxis reaction to cefuroxime with cross-reactivity with cefotaxime. *Ann Allergy Asthma Immunol.* 2002; 89: 101-103.
- 80 Romano A, Gaeta F, Valluzzi RL, et al. IgE-mediated hypersensitivity to cephalosporins: Cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol.* 2015; 136: 685-691.
- 81 Moreno E, Davila I, Laffond E, et al. Selective immediate hypersensitivity to cefepime. *J Investig Allergol Clin Immunol.* 2007; 17: 52-54.
- 82 Romano A, Viola M, Gueant-Rodriguez RM, et al. Imipenem in patients with immediate hypersensitivity to penicillins. *N Engl J Med.* 2006; 354: 2835-2837.
- 83 Romano A, Viola M, Gueant-Rodriguez RM, et al. Brief communication: tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillins. *Ann Intern Med.* 2007; 146: 266-269.
- 84 Atanaskovic-Markovic M, Gaeta F, Medjo B, et al. Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. *Allergy.* 2008; 63: 237-240.
- 85 Atanaskovic-Markovic M, Gaeta F, Gavrovic-Jankulovic M, et al. Tolerability of imipenem in children with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol.* 2009; 124: 167-169.
- 86 Gaeta F, Valluzzi RL, Alonzi C, et al. Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol.* 2015; 135: 972-976.
- 87 Romano A, Gaeta F, Valluzzi RL, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. *J Allergy Clin Immunol.* 2010; 126: 994-999.
- 88 Romano A, Gaeta F, Valluzzi RL, et al. Absence of cross-reactivity to carbapenems in patients with delayed hypersensitivity to penicillins. *Allergy.* 2013; 68: 1618-1621.
- 89 Gonzalo-Garjito MA, Rodriguez-Nevaldo I, de Argila D. Patch tests for diagnosis of delayed hypersensitivity to cephalosporins. *Allergol Immunopathol (Madr).* 2006; 34: 39-41.
- 90 Schiavino D, Nucera E, Lombardo C, et al. Cross-reactivity and tolerability of imipenem in patients with delayed-type, cell-mediated hypersensitivity to beta-lactams. *Allergy.* 2009; 64: 1644-1648.
- 91 Noguero-Mellado B, Pinto Fernandez C, Pineda-Pineda R, et al. Cross-reactivity between carbapenems: two case reports. *J Allergy Clin Immunol Pract.* 2014; 2: 816-817.
- 92 Chen Z, Baur X, Kutscha-Lissberg F, et al. IgE-mediated anaphylactic reaction to imipenem. *Allergy.* 2000; 55: 92-93.
- 93 Moss RB. Sensitization to aztreonam and cross-reactivity with other beta-lactam antibiotics in high-risk patients with cystic fibrosis. *J Allergy Clin Immunol.* 1991; 87: 78-88.
- 94 Perez Pimiento A, Gomez Martinez M, Minguez Mena A, et al. Aztreonam and ceftazidime: evidence of in vivo cross allergenicity. *Allergy.* 1998; 53: 624-625.