ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Cross-reactivity among beta-lactams: a practical approach

Reatividade cruzada entre betalactâmicos: uma abordagem prática

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ABSTRACT

Beta-lactams are the drugs most commonly involved in hypersensitivity reactions mediated by a specific immune mechanism and are the main triggers among antibiotics. They include penicillins, cephalosporins, carbapenems, monobactams and beta-lactam inhibitors. The basic chemical structure of these drugs consist on the presence of the following components: beta-lactam ring, an adjacent ring and side chains, all of which are potential epitopes. IgE antibodies and T lymphocytes are often involved in recognizing those epitopes. Cross-reactivity depends on the stability of intermediate products (antigenic determinants) derived from the degradation of the beta-lactam ring, on the adjacent rings, and on the structural similarity of the side chains between drugs. Classically, it was believed that there was a

RESUMO

Os betalactâmicos são a classe de drogas que mais causam reações de hipersensibilidade envolvendo um mecanismo imunológico específico, e são os principais desencadeantes entre os antimicrobianos. São representados pelas penicilinas, cefalosporinas, carbapenêmicos, monobactâmicos e inibidores da betalactamase. A estrutura química básica destes fármacos consiste na presença dos seguintes componentes: anel betalactâmico, anel adjacente e cadeias laterais, sendo todos potenciais epítopos. Os anticorpos da classe IgE e linfócitos T estão frequentemente envolvidos no reconhecimento desses epítopos. A reatividade cruzada depende da estabilidade dos produtos intermediários (determinantes antigênicos) derivados da degradação dos anéis betalactâmicos, anéis adicionais e da semelhança estrutural das

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great potential for cross-reactivity within each class and even between classes, but studies from the last decade showed that individuals allergic to penicillin (with positive skin tests) reacted to cephalosporins in approximately 3% of cases, to carbapenems in about 1%, and rarely reacted to monobactams. This reactivity or tolerance seems to be linked to the degree of similarity between the side chains of these antibiotics. In this review, we emphasize the importance of systematic investigation to confirm or exclude allergy to beta-lactams, we describe the prevalence of cross-reactivity between these drugs and we suggest an algorithm for approaching these patients based on their chemical structure and on data published in the literature.

Keywords: Beta-Lactams, penicillins, cephalosporins, drug hypersensitivity.

cadeias laterais entre as drogas. Classicamente acreditava-se num grande potencial de reatividade cruzada dentro de cada classe e até entre as classes, mas estudos da última década mostraram que indivíduos alérgicos à penicilina (com testes cutâneos positivos) reagiam às cefalosporinas em aproximadamente 3% dos casos, aos carbapenêmicos em cerca de 1%, e praticamente não reagiam aos monobactâmicos. Essa reatividade ou tolerância parece estar vinculada ao grau de similaridade entre as cadeias laterais desses antibióticos. Nesta revisão, ressaltamos a importância da investigação sistematizada na confirmação ou exclusão de alergia aos betalactâmicos, descrevemos a prevalência da reatividade cruzada entre estes fármacos e sugerimos um algoritmo de abordagem desses pacientes baseados em sua estrutura química e nos dados publicados na literatura.

Descritores: Betalactamas, penicilinas, cefalosporinas, hipersensibilidade a drogas.

Introduction

Antibiotics are among the most prescribed drugs in the world in healthcare institutions.1 Beta-lactams (BL) are considered essential in the treatment for various situations such as: pharyngitis and skin infections caused by group A Streptococcus; meningitis and puerperal sepsis caused by group B Streptococcus; endocarditis by Streptococcus of the Viridans group; syphilis, particularly in pregnant women; osteomyelitis and skin infections caused by *Staphylococcus aureus*, among others.[2] Approximately 10% of the US population reports allergy to penicillin, but for the most part the signs and symptoms referred to are non-specific such as gastrointestinal symptoms, pruritus without lesions, undefined reactions that occurred more than 10 years ago or a family history of BL allergy, which rarely configure true hypersensitivity reactions. Only about 5% of all patients with a history of allergy to BL have their reactions confirmed after a systematic investigation as hypersensitivity reactions, either immediately involving IgE class antibodies or late mediated by T lymphocytes.[2,3] The BL allergy label is a public health problem with the following repercussions: increased use of second-line or broader-spectrum antimicrobials, increased microbial resistance (Multi-resistant Staphylococcus, Vancomycin-resistant Enterococcus), greater toxicity and increased costs (longer hospital stays and readmissions).[2,4] Only about 5% of all patients with a history of allergy to BL have their reactions confirmed after a systematic investigation as hypersensitivity reactions, either immediately involving IgE class antibodies or late mediated by T lymphocytes.[2,3] The BL allergy label is a public health problem with the following repercussions: increased use of second-line or broader-spectrum antimicrobials, increased microbial resistance (Multi-resistant Staphylococcus, Vancomycin-resistant Enterococcus), greater toxicity and increased costs (longer hospital stays and readmissions).[2,4]

Our group recently published a comprehensive review on BL hypersensitivity.[5] To carry out this update focused on the cross-reactivity between the antibiotics in the group, searches were performed for original articles, reviews, guidelines and consensus in the MEDLINE and Latin American and Caribbean Literature in Health Sciences (LILACS) databases, using the terms: *beta-lactams hypersensitivity*, *beta-lactam cross-reactivity*, *penicillins*, *cephalosporins*, *carbapenems*, *monobactams*, *diagnostic tests*, *risk stratification*.

Chemical structure of beta-lactams

BL are the antimicrobials most implicated in drug hypersensitivity reactions involving a specific immune mechanism.[6-8] The main classes of BL according to their chemical structures are: penicillins, cephalosporins, carbapenems and monobactams. The basic chemical structure of BLs consists of the presence of the following components: BL ring, adjacent ring and side chains; which are potential immunogenic sites capable of triggering sensitization of lymphocytes to BL. Penicillins contain the BL ring, an adjacent ring (thiazolidine) and an R1 side chain that communicates with the BL ring. Cephalosporins have the BL ring, another adjacent ring (dihydrothiazine) and two side chains R1 and R2, with R1 also binding to the BL ring (similar to penicillins) and R2 communicating with the adjacent ring. Carbapenems have the BL ring, an adjacent ring (dihydropyrrole) and two side chains R1 and R2. Monobactams, on the other hand, have only the BL ring associated with an R1 side chain. Finally, some authors consider that the clavulanic acid beta-lactamase inhibitor would be a fifth class of BL, and this antibiotic does not have an adjacent ring. As this drug is only available on the market in association with aminopenicillins, this classification into five classes is not consensual in the literature. The chemical structure of the BL classes is outlined in Figure 1.[5]

Immune mechanisms

Cross-reactivity between different BLs has been reported in studies, and its approach needs to be done in the context of knowledge of the immunological mechanisms involved. Hypersensitivity reactions to BL occur mainly through the production of IgE class antibodies, activation of T lymphocytes and also direct pharmacological interaction with protein receptors on cells (HLA and TCR).[7] It is believed that IgE class antibodies and lymphocytes T recognize as epitopes some segment of the BL chemical structure.

BL are small molecules that bind to plasma proteins forming hapten-carrier complexes. Immunoreactivity against a BL depends on the stability of intermediate products (antigenic determinants) arising from the degradation of BL rings and adjacent rings. The determinants of penicillins are stable and well defined, while the determinants of cephalosporins are not well known.[8] The main determinants or PPL (peniciloyl poly-lysine) correspond to 95% of these metabolites and the secondary or MDM (penicilloate and peniloate) to approximately 5%.

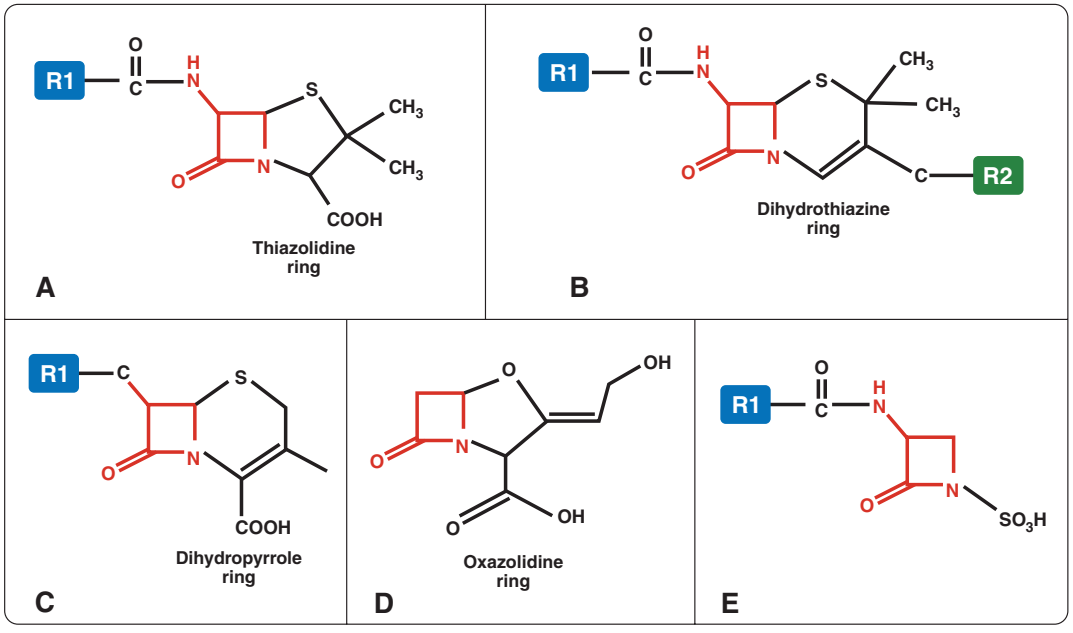


Figure 1
Basic chemical structure of the five classes of beta-lactams.
Source: Felix M. et al.[5]

It is postulated that these determinants bind to carrier plasma proteins and can stimulate the immune response.[2] Antibodies of the IgE class can bind to the BL ring, adjacent ring or side chains and form the basis of cross-reactivity involving penicillins, justifying the use of skin tests in the systematic investigation of immediate reactions to these drugs. However, more recently, it has been demonstrated that cross-reactivity between BL is mainly triggered by the similarity or structural identity between the side chains of these drugs, suggesting that this segment is the epitope in most hypersensitivity reactions.[9-12]

Penicillins and cephalosporins are the two classes of BL that most cause hypersensitivity reactions, both immediate and late, involving practically all the mechanisms described by Gell and Coombs.[12] The main immunological mechanisms involved in BL hypersensitivity are summarized in Table 1.

Clinical manifestations

Immediate reactions by IgE class antibodies usually occur within the first hour after exposure to the drug, although it may occur within 6 hours, but tends to occur earlier after re-exposure. Cutaneous manifestations such as urticaria, angioedema, pruritus and flushing-type erythema are the most frequent. Other immediate manifestations include: respiratory symptoms (rhinorrhea, nasal congestion, cough, dyspnea, hoarseness); gastrointestinal (diarrhoea, vomiting and abdominal pain); cardiovascular (hypotension, tachycardia), and more severe conditions with association of systemic signs and symptoms (anaphylaxis).[2]

Late manifestations mediated by T lymphocytes usually occur more than 1 to 6 hours after exposure to the drug, appearing more commonly after the first 24 hours of starting treatment. Maculopapular rash is the

Table 1
Immunological mechanisms in hypersensitivity reactions to beta-lactams.

Mechanism (modified Gell and Coombs)	Type of immune response	Pathological features	Clinical examples
Type I	Ige	Mast cell degranulation	Anaphylaxis, urticaria, angioedema, asthma, rhinitis
Type II	IgG and FcR	FcR-dependent cell death	Hemolytic anemia
Type III	IgG, complement and FcR	Immune complex deposition	Serum sickness
Type IVa	TH1 (IFN-gamma)	Monocyte activation	Contact eczema
Type IVb	TH2 (IL-4 and 5)	Eosinophilic inflammation	EMP, DRESS(?)
Type IVc	Cytotoxic T	CD4 or CD8-dependent cell death	SSJ/NET, EFD
Type IVd	T cell (IL-8)	Neutrophil activation	HANDLE
Type IVe	T cell (IL-12, IFN-gamma)	Activating CD4 or CD8	"Accelerated" urticaria
Undefined	T cell	TH1 and TH2 complex patterns	DRESS
Specific organ	T cell	Complex mechanisms	Hepatitis, pneumonitis

Ig = immunoglobulin, FcR = receptor for Fc fraction, TH = T-helper, IFN = interferon, IL = interleukin, EMP = maculopapular rash, DRESS = drug rash with eosinophilia and systemic symptoms, SSJ = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, EFD = fixed drug eruption, PEGA = acute generalized exanthematic pustulosis.
Modified from Blanca-Lopez N. et al.[12]

most frequent reaction, but severe manifestations such as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematic pustulosis (PEGA), drug reaction with eosinophilia and systemic symptoms (DRESS) also known as drug-induced hypersensitivity syndrome (SHID) can also occur.[2,13,14]

Diagnostic investigation

This review of current studies of cross-reactivity among BL addresses systematic investigation using the following diagnostic tools: in vitro tests where available, immediate or delayed reading skin tests, and provocation tests, which are the gold standard for confirming or ruling out the drug involved in the reaction and finding a safe alternative drug among BL.

Hypersensitivity reactions to BL should be addressed in a systematic way, through a detailed clinical history followed by immediate reading skin tests (prick and intradermal) or delayed reading skin tests (contact test and/or late reading intradermal skin test). BL contact tests are performed in 5% petroleum jelly, but the concentration for puncture and intradermal varies between medications. Table 2 summarizes the non-irritant concentrations used in puncture and intradermal tests with these drugs.[5] The negative predictive value of skin tests when using PPL and MDM is greater than 93% and the positive predictive value is around 50 to 75%.[2] Individuals with negative skin tests may be submitted to the provocation test after risk stratification.[2]

In vitro tests can be used to complement the investigation when available. In immediate reactions, the following can be used: tryptase, specific IgE dosages and the basophil activation test (BAT). Tryptase in the acute phase may indicate whether mast cell degranulation has occurred, and when elevated it indicates that there was an anaphylactic-type reaction; basal tryptase should be evaluated to rule out the possibility of increase due to systemic mastocytosis or other non-clonal mast cell disorders. Specific IgE dosages for BL have a low sensitivity and are available for some drugs (Penicillin G and V, amoxicillin, ampicillin and cefaclor). The main use of specific IgE dosage would be in patients at high risk for severe immediate reactions (anaphylaxis) before performing skin and provocation tests. BAT quantifies drug-induced CD63 or CD203c expression using flow cytometry, but it is only available in a few specialized centers and its greatest indication would also be in high-risk immediate reactions prior to the performance of the challenge test. In late reactions, lymphocyte transformation (TTL) and ELISPOT (enzyme-linked immunosorbent spot assay) tests can be useful in evaluating these reactions. The TTL

Table 2
Maximum non-irritant concentrations for skin tests (puncture and intradermal) with beta-lactams.

Hapten (drug)	Puncture and intradermal
Benzylpenicillin	10,000 UI/mL
Amoxicillin	20 mg/mL
Ampicillin	20 mg/mL
Cefepime	2 mg/mL
Other cephalosporins	20 mg/mL
Imipenem	0.5 mg/mL
Meropenem	1 mg/mL
Aztreonam	2 mg/mL

Source: Felix M. et al.[5].

measures the proliferation of T lymphocytes in the presence of the suspected drug over a period of 5 to 7 days and the ELISPOT detects cells producing antigen-specific cytokines after incubation with polymorphonuclear cells for 24 hours in the presence of the suspected drug. BAT and assays for late reactions, in our environment, are still only used at the research level.[2,13,15]

Risk stratification

Risk stratification must be approached taking into account the characteristics of the initial clinical manifestations of the suspected drug and the presence of comorbidities in the patient. It can be classified as low, moderate and high risk. Table 3 shows the main clinical aspects related to BL risk stratification.[5,15] Cardiovascular, renal and respiratory

Table 3
Risk stratification in beta-lactam hypersensitivity.

Risk level	Clinical classification of reaction	Clinical picture of the reaction
High risk	Immediate reactions	– Anaphylaxis – Hypotension – Laryngeal edema – Bronchospasm – Urticaria and/or angioedema – Generalized erythema
High risk •	Non-immediate reactions	– SSJ/NET – DRESS – HANDLE – Fixed generalized drug eruption bullous – IgA bullous dermatosis – Severe maculopapular rash (confluent rash and evolution to erythroderma; duration > 1 week; fever, eosinophilia) – Serum disease simile – Organ-specific manifestations (cytopenias, nephritis, hepatitis, pneumonitis) – Drug-induced autoimmune diseases (lupus, pemphigus vulgaris, bullous pemphigoid)
Low risk	Immediate reactions	– Isolated generalized itching – Isolated gastrointestinal symptoms (nausea, vomiting, diarrhea) – Localized urticaria
Low risk	Non-immediate reactions	– Contact dermatitis – Local reaction to IM administration – Palmar exfoliative rash – Fixed drug eruption – Late-onset urticaria – Mild to moderate maculopapular rash (especially in children) – SDRIFE

DRESS = drug rash with eosinophilia and systemic symptoms, IM = intramuscular, TEN = toxic epidermal necrolysis, IgA = immunoglobulin A, PEGA = acute generalized exanthematic pustulosis, SDRIFE = symmetrical drug-related intertriginous and flexural exanthema, SSJ = Stevens Johnson syndrome.
Source: Felix M. et al.[5].

diseases in activities; the use of drugs such as beta-blockers, antiarrhythmics, ACE (angiotensin-converting enzyme) inhibitors; Systemic mastocytosis and even the presence of pregnancy are potential high-risk situations. In the context of BL risk stratification, the two most frequent practical scenarios are also the most debated in the assessment of hypersensitivity and cross-reactivity between BL: patients allergic to penicillins or those allergic to some cephalosporins.[16-20]

Knowledge of the basic structure of BL, taking into account the similarity and identity between these drugs in the context of cross-reactivity, becomes essential in choosing an effective and safe alternative drug during the investigation, as recommended by the main studies.[17-21] Table 4 summarizes the BLs available in the Brazilian market that have similar or identical R1 or R2 side chains.

Allergic to penicillin: cross-reactivity to aminopenicillins

Despite the large number of patients labeled as allergic to penicillin, more than 95% can tolerate penicillin after systematic investigation. Due to this low prevalence of true penicillin allergy, individuals with a history of penicillin reactions should be evaluated to confirm or rule out this diagnosis, thus avoiding the use of broad-spectrum alternative drugs from other classes, such as vancomycin and quinolones, which elevate the costs, increase the selection of resistant strains such as *Enterococcus* and *Staphylococcus aureus* resistant to vancomycin and *Clostridium difficile*.[4,21,22]

Studies report a high cross-reactivity between benzylpenicillin and semi-synthetic penicillins, more precisely the aminopenicillins (amoxicillin and ampicillin), as they share the amino group in the R1 side chain.[15,17,19,23]

On the other hand, studies with individuals allergic to aminopenicillins, who presented reactions mediated by IgE or even delayed, showed negative skin tests for benzylpenicillin (penicillin G) and phenoxymethylpenicillin (penicillin V) and tolerance to provocation with these drugs. Blanca-Lopez et al. studied 58 individuals with immediate reactions to amoxicillin or amoxicillin/clavulanic acid. Of these, 7 were positive for penicillin determinantsG, 40 were positive to amoxicillin, but tolerated penicillins G and V, and 11 were positive only to clavulanic acid, tolerating penicillin G, V and amoxicillin.[24] Torres et al. diagnosed immediate hypersensitivity to penicillins in 290 patients through skin tests, specific IgE dosages or provocation tests, with amoxicillin involved in 65% of cases and benzylpenicillin in 3%. In that sample: 58% were considered selective reactors to aminopenicillins (amoxicillin or ampicillin) and the other 42% were also positive for the PPL or MDM determinants, being classified as non-selective responders.[25] Regarding late reactions to aminopenicillins, another study showed that 72% of these patients tolerated penicillin V.[26]

Table 4
Summary of beta-lactams available in the Brazilian market that share some similarity between the R1 or R2 side chains.

Similar or identical R1 chain	Similar or identical R2 chain
Benzylpenicillin, Amoxicillin, Ampicillin, Piperacillin, Cephalexin, Cefaclor and Cefadroxil	Cephalexin and Cephadroxil
Cephalotin and Cefoxitin	Cephalotin, Cefuroxime, Cefoxitin and Cefotaxime
Ceftriaxone, Cefuroxime, Cefotaxime, Ceftazidime, Cefepime, Ceftaroline and Aztreonam	

Modified from Chaudhry S.B. et al.[20]

Penicillin allergic: cross-reactivity with cephalosporins

Some previous studies showed conflicting data with current studies in patients allergic to penicillin and cross-reactive to cephalosporins. It is believed that the contamination of cephalosporins with penicillin G traces in their chemical processing led to an overestimation of the prevalence of cross-reactivity between these classes of BL.[2] In studies carried out from 1990 onwards in patients with proven IgE-mediated reactions to penicillins, the rate of positivity to cephalosporin skin tests ranged from 0 to 27%,[27] however, more recent data suggest that the rates should actually vary from according to the similarity of the R1 side chain between penicillins and cephalosporins.

Caimmi S. et al. evaluated the safety of cefuroxime in patients with proven hypersensitivity to one or more BL. Of the 143 allergic individuals evaluated, the prevalence of sensitization to cefuroxime in patients allergic only to penicillins was 4.2%, showing that it is a safe alternative drug to be used after carrying out tests in this group of individuals.[28] Importantly, cefuroxime has an R1 chain quite distinct from the R1 chains of penicillins.

In 2018, Professor Antonino Romano's group published a large series, in which they studied 252 individuals with IgE-mediated allergy to penicillins in relation to cephalosporin reactivity. To do so, they used an extensive algorithm that included IgE measurement for cefaclor, skin tests and challenge with cephalosporins of varied structures. We found 99 (39.3%) people with some positive test for cephalosporins, but almost all were positive for cephalosporins with R1 chains identical or similar to those of penicillins. No patient responded to the challenge with cefuroxime and ceftriaxone, which do not share R1 with penicillins. Therefore, it was concluded that individuals with IgE-mediated allergy to penicillins may undergo treatment with distinct R1 chain cephalosporins, but who preferentially have negative tests for these antibiotics before therapeutic administration.[27]

Confirming these findings, in a recent meta-analysis of 21 studies, Picard M. et al. included 1,269 patients who were known to be allergic to penicillin (IgE- or T-lymphocyte-mediated reactions) and showed that the cross-reactivity index varies with the degree of similarity between the R1 side chains. This risk was 16.5% for some aminocephalosporins with side chains identical to aminopenicillins, 5.6% for cephalosporins that had R1 side chains similar to penicillins, and 2.1% for other cephalosporins with a low degree of chemical similarity to the aminopenicillins.[18]

As examples, we bring two clinical cases of patients from the UPM author's personal file. In the first case, a patient with a history of immediate urticaria after exposure to amoxicillin. In the investigation, she presented a positive skin test for penicillin G and amoxicillin-clavulanate, denoting the likely cross-reactivity due to the similarity of the R1 side chains (Figure 2). The patient underwent supervised oral challenge with cefaclor, which has a similar but not identical R1 chain, and she had good tolerance to this drug. However, it is necessary to emphasize that, as it is an antibiotic with a similar chain, it was only possible to release cefaclor after complete investigation until negative provocation. The risk of reaction to this drug would be, initially, higher than that of another cephalosporin of a different R1 chain, such as cefuroxime, for example, which was the drug used in the second case – another patient, with a history of immediate urticaria and angioedema after exposure to amoxicillin. Skin tests were performed with penicillins (Figure 3), and, as an alternative, with cefuroxime, whose R1 side chain is completely different. The intradermal test with this cephalosporin was negative, and tolerance was subsequently proven with a negative challenge test.

Romano A et al. studied 131 patients with immediate reactions (mostly anaphylaxis to penicillins) confirmed with positive skin tests. All underwent skin tests with cefazolin and ceftibuten, cephalosporins that do not share the R1 chain with penicillins, and tolerance was subsequently confirmed through challenge. Only one patient (0.8%) had a positive skin test for cefazolin and ceftibuten and also for other reagents such as carbapenem and aztreonan, suggesting that, for this patient, the antigenic determinant was the BL ring itself. The findings confirm that the epitope must, in most cases, be related to the side chain. However, due to the possibility, although remote, of sensitization to the BL ring or even cosensitization to different BL, the authors maintained the recommendation to perform pretreatment skin tests with these cephalosporins in those sensitized to penicillins.[29]

Some studies evaluated cross-reactivity with cephalosporins in patients with late allergic reactions to penicillins and a cross-reactivity of up to 31.2%[15] was described, however, in a more systematic investigation, using a cephalosporin panel, Romano

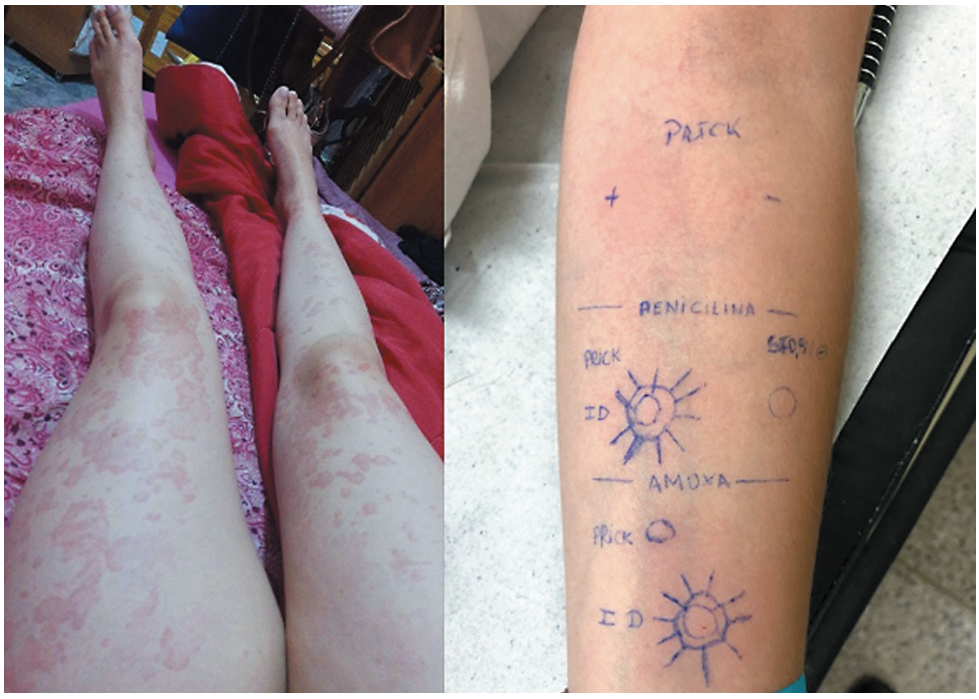


Figure 2
Immediate reaction to amoxicillin (urticaria) and positive immediate-reading intradermal test to amoxicillin-clavulanate and penicillin.

et al. studied patients with T lymphocyte-mediated reactions to penicillins confirmed by late skin prick tests, both intradermal late read and patch test. Individuals were submitted to these same skin tests with cephalosporins, and, when negative, to provocation tests. In that study, the overall cross-reactivity rate between aminopenicillins and aminocephalosporins (cephalexin, cefaclor, cefadroxil) was around 20%, but it was zero with cefuroxime and ceftriaxone. It is worth remembering that the three studied aminocephalosporins have R1 side chain similar or identical to aminopenicillins. These data corroborate the fact that, in late allergic reactions, the antigenic determinant is the side chain.[30]

Allergic to penicillins: cross-reactivity with carbapenems and monobactams

In patients with confirmed IgE-mediated reactions to penicillin, the cross-reactivity index with carbapenems was less than 1% in skin tests performed for imipenem, meropenem and ertapenem.[31] In another study involving 212 patients with confirmed IgE antibody reactions to penicillins, all had negative skin tests to aztreonan, and 211 were negative to the aztreonam challenge test.[32]

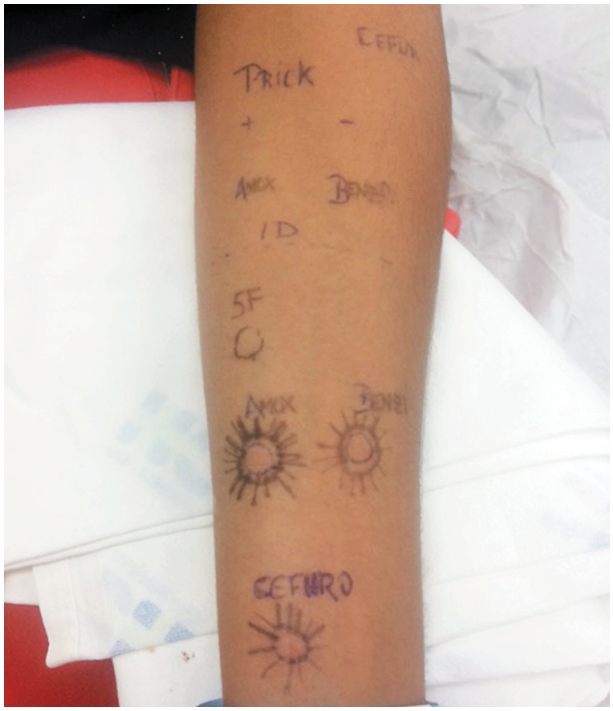


Figure 3
Positive intradermal skin tests with penicillin and amoxicillin-clavulanate and negative with cefuroxime in a patient with a history of immediate urticaria and angioedema after amoxicillin.

As for non-immediate reactions to penicillins, two studies published by the same group, in which more than two hundred patients were studied, showed 100% of negative skin and provocation tests with carbapenems and aztreonam.[30,33] These data confirm the findings that side chains must be the antigenic determinant of all late reactions to BL.

Cephalosporins: cross-reactivity with penicillins

Hypersensitivity reactions to cephalosporins are reported in about 1-3% of the population, but in Europe it accounts for 10 to 40% of all reactions to BL and also as an important cause of perioperative anaphylaxis, especially cefazolin.[8,20]

In individuals with IgE-mediated allergy to cephalosporins, few studies have evaluated cross-reactivity with other BL using challenge testing in individuals with negative skin tests. In a study with 24 patients allergic to cephalosporins, only 2 patients had positive skin tests to penicillin G, the remaining 22 patients with negative tests tolerated penicillin G challenge.[34] Another study carried out in 40 patients with anaphylaxis to cefazolin, confirmed by skin tests, without skin tests for penicillin and submitted to oral challenge with amoxicillin for 3 days, did not show any immediate reaction, and only 1 patient had a late benign rash after 24 hours of provocation.[35]

Cephalosporin allergy: cross-reactivity with carbapenems and monobactams

Few studies have studied the cross-reactivity between cephalosporins, carbapenems and monobactams. In a systematic review published in 2014, the authors compiled data from 10 studies and 12 case reports, resulting in an additional 850 individuals, but only 12 had a history, and not confirmed, of immediate reactions to cephalosporins. In this group, the incidence of reactions to carbapenemics was 25% (3 patients).[36]

In another study by prof. Romano, 98 patients allergic to cephalosporins were evaluated. The positivity for tests with these other BL was low: 2% for imipenem, 1% for meropenem and 3.1% for aztreonam, with emphasis on the latter for patients whose previous allergy was to ceftazidime, which shares R1 chain like this monobactam.[37]

In summary, in patients allergic to cephalosporins, cross-reactivity with carbapenems is less than 1%, and practically non-existent with monobactams, except in patients allergic to ceftazidime, which has a side chain identical to aztreonam.[8,16]

Cephalosporin allergy: cross-reactivity with other cephalosporins

In evaluating patients who are allergic to cephalosporins, an important question is whether they are able to tolerate other cephalosporins. In those allergic to cephalosporins, the IgE-mediated immune response is commonly directed to the R1 and R2 side chains, implying that these patients can tolerate other cephalosporins with different side chains. However, this evidence is still based on few studies of small series and case reports, in addition to having been described as cosensitization to cephalosporins, or even less frequently due to sensitivity to an antigenic determinant related to the BL ring. Cross-reactivity between cephalosporins has been demonstrated by similarity or identity mainly between the R1 side chains, but also in relation to the R2.

Few studies have been performed in patients allergic to cephalosporins who were challenged with alternative cephalosporins that showed negative skin tests. In a study involving 21 patients with immediate reactions to cefazolin, 19 with anaphylactic reactions, all had negative skin tests to cephalotin and also tolerated the challenge with this drug.[38] And in another study, patients with a history of immediate reaction to cefuroxime, and confirmed with positive skin tests, underwent skin tests for ceftazidime. All had negative results and tolerated the challenge with this drug, showing that a small structural difference between these drugs can result in a loss of cross-reactivity and present clinical tolerance.[39]

Another larger study involved 102 patients with a history of immediate reactions to cephalosporins, both anaphylaxis and urticaria. All underwent skin tests with a panel of 11 cephalosporins and were classified into 4 groups according to the response to the tests.[40]

– *Group A:* 73 patients with positive skin tests to ceftriaxone or another cephalosporin with a similar R1 side chain (cefotaxime, ceftazidime, cefuroxime, cefodizime);

- *Group B:* 13 patients who tested positive for aminocephalosporins with R1 side chains identical to amoxicillin or ampicillin (cephalexin, cefaclor and cefadroxil);
- *Group C:* 7 patients with similar R1 side chains (cefazolin, cefoperazone, cefamandole);
- *Group D:* 9 patients with cephalosporin positivity from more than one group, suggesting an immune response directed at the BL rings or dihydrothiazine, rather than the side chains.

Systematized challenge was performed with selected cephalosporins, whose skin tests had been negative, and there was no reaction. No patient was challenged with a similar R1 side chain cephalosporin or with the cephalosporin involved in the reaction. Challenges with alternative cephalosporins were, in general, well tolerated, confirming that the allergy would not be "class specific", but rather, in most cases, directed to the R1 or R2 chains. Furthermore, the authors concluded that the negative skin tests before the challenges were already an excellent biomarker of the safety of the challenge, which would later be confirmed as negative.[40]

Anyway, it is notorious that the studies that evaluated the cross-reactivity within the cephalosporin class are still scarce and should grow exponentially in the next ones, due to the growing importance of this BL class in clinical practice. In what may be the largest single-center series of patients investigated for suspected cephalosporin allergy, Touati N. et al. retrospectively surveyed data from 476 patients with a history of reactions to cephalosporins. Allergy was confirmed in only 22.3% of cases, 51.9% using skin tests and 48.1% using provocation tests. Despite being safe, provocation tests triggered anaphylaxis in 20% of cases, and even skin tests caused systemic reactions in 9.1% of individuals. Patients were investigated to confirm or exclude the causative agent and were also classified into 4 groups according to the R1 side chain, but there was no systematic investigation of cross-reactivity. Even within groups of similar or identical R1 chains, the cross-reactivity index was very low.[41]

Current recommendations - EAACI (European Academy of Allergy and Clinical Immunology)

Considering existing studies until 2020, the EAACI recently published guidelines to facilitate the management of patients with allergy to one or more BL. In that publication, sensitization to the BL ring in IgE-mediated reactions was defined as "very rare", with the side chains being the most frequent epitope. In addition, it was also described that, in reactions by cellular immunity, sensitization to the BL ring does not occur, that is, the cross-reactivity between all BLs is non-existent and, therefore, the exchange of BL for another with a different side chain is safe.[15]

As recommendations regarding the two most used classes, penicillins and cephalosporins, the European guidelines suggest that, in patients who cannot undergo a full investigation, when there is an indication for a cephalosporin in an individual with a history of immediate allergy to penicillin, that it be submitted to skin tests with cephalosporins of side chains other than penicillins and, if the results are negative, submitted to a provocation test.[15] On the other hand, in mild to moderate non-immediate reactions (rash) to penicillins in patients who require treatment with cephalosporins and there is no time to perform pre-treatment late-reading skin tests, administration of a full dose of cephalosporins with side chains other than penicillins under medical supervision, with no risk of serious reactions, but only the occurrence of rash being documented.[15]

In the Brazilian reality, where the performance of skin tests with drugs is the scope of the practice of the allergist-immunologist and taking into account that our specialty does not yet have qualified and available professionals equally distributed throughout the country, we believe that this algorithm can be adapted to our reality, in order to become more practical and feasible throughout the national territory.

Current recommendations – Scientific Department of Drug Allergy at ASBAI

Initially, in a suspected previous allergy to a BL, one should ask about the urgency of the investigation. Ideally, the investigation should be started as soon as possible, respecting the minimum interval of 4 weeks after the initial reaction, if possible.

If the investigation is elective and outpatient, the priority should be to try to confirm or exclude hypersensitivity to the suspected BL. However, at the same time, investigation of other members of the same class can be used, particularly in skin tests, in which several tests can be performed at the same time and also assess tolerance to other BL antibiotics,

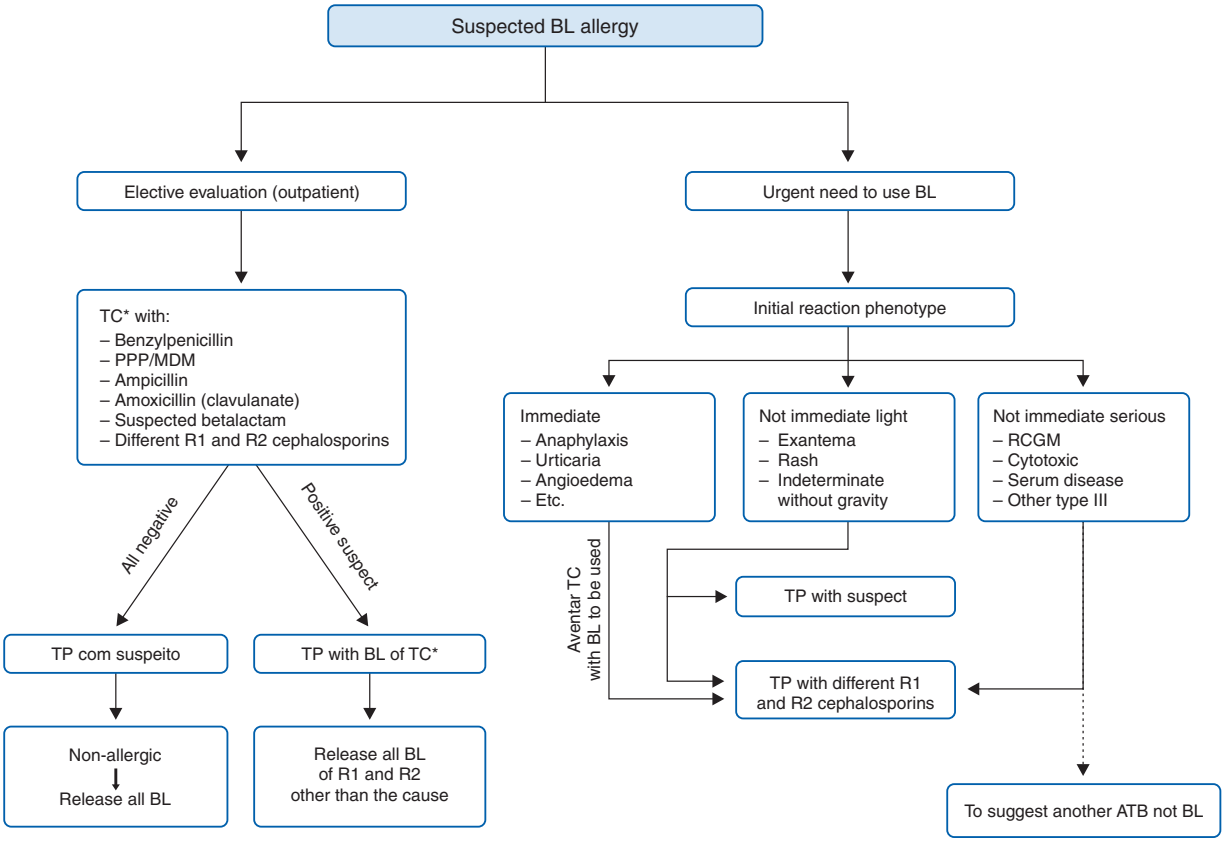
if the suspect is confirmed as guilty. For this purpose, the method of initially characterizing the phenotype of the index reaction and whether it was immediate or not immediate must be respected, in order to perform the appropriate skin test: puncture and intradermal immediate reading or intradermal semi-late reading [Arthus] or late and contact test, respectively. In addition, it is imperative to remember that to perform intradermal, medications must be used in their sterile injectable (parenteral) presentations.

If the skin tests are negative and there is no contraindication, based on the patient's risk stratification, the ideal is to carry out the challenge with the suspect, because if this is negative, the entire BL class will be free for use. We also emphasize that, in case of non-immediate mild exanthematic reactions, provocation can be used directly, without the obligation of skin tests. However, if the initial BL allergy is confirmed, either by skin or provocation test, or if there is any contraindication (severe pharmacoderma, for example), alternatives can be released with the provocation test based on the side chains of the drug.

If there is an urgent need for the use of BL in a patient not yet investigated, the systematic investigation will have to be postponed and the priority will be the release of an effective and safe BL. In this case, the rule is to use BL with a structure different from the one suspected of having caused the initial reaction (Table 4) and, ideally, to carry out the first administration with increased doses, as in a provocation test. In the case of an immediate initial reaction, particularly if it has been anaphylactic, immediate-read skin tests with the alternative BL before the first therapeutic dose may increase the safety of this challenge. At the end of treatment with this BL, a complete investigation of the suspected agent should be scheduled, in order to de-label possible non-allergic patients and release the entire BL class. The suggested algorithm for assessing tolerance to other BL in a patient with suspected allergy is outlined in Figure 4.

Conclusions

Beta-lactams are the drugs that most cause hypersensitivity reactions involving an immunological mechanism, with emphasis on the classes of penicillins and cephalosporins. Recent studies have shown that both within the same class and between beta-lactams from different classes, cross-reactivity is much lower than previously thought, and seems to be closely related to the structural similarity between the side chains of these drugs. Thus, knowledge of the chemical structure of beta-lactams is essential in this assessment. The updated approach to cross-reactivity between beta-lactams should be done through a systematic investigation, allowing for the dislabeling of patients who are not truly allergic, but at least allowing the use of an alternative beta-lactam in a safe and effective way. The development of educational programs, with the standardization of algorithms between different centers that allow specialist and non-specialist physicians to put into practice the most appropriate administration of antimicrobials in intra and extra-hospital environments.



BL = beta-lactam, TC = skin test, BP = benzylpenicillin, PPL = peniciloyl polylysine, MDM = mixture of secondary determinants, R1/R2 = side chains, TP = provocation test, TC = skin test, RCGM = severe skin reaction to drug , ATB = antibiotic.

* Before indicating the skin test, it is mandatory to define the reaction phenotype. Immediate reactions should be investigated with a puncture test and, if negative, with an intradermal test, both immediately read, with the medications properly diluted, and being used in their injectable presentations. Non-immediate reactions can be investigated by intradermal, but with semi-late (Arthus, 6 to 8 hours) or late (48 to 72 hours) readings, or by the classic patch test (48 and 96 hours readings and sometimes, 7 days). If available, major and minor determinants of penicillin can be used for puncture and intradermal.

Figure 4

Algorithm for analysing the patient with suspected allergy to a beta-lactam, in order to investigate the cause and possible tolerance to other antibiotics of the class.

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