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Drug Allergy (MJ Torres Jaén, Section Editor)

Cross-Reactivity in Betalactam Allergy: Alternative Treatments

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Opinion statement

It was originally thought that, as all betalactams share a four-member ring, they would cross-react, and so the classical recommendation was for allergic patients to avoid all betalactams. However, later studies found that some individuals selectively responded to one betalactam only and tolerated others. This was shown to be more frequent than initially thought, and this finding has led to a change from the initial recommendations of complete avoidance. Selective responses to amoxicillin are mainly due to recognition of the side chain structure, making benzylpenicillin a safe alternative. These amoxicillin-selective responders comprise up to 55 and 90 % of patients with immediate allergic reactions to amoxicillin and amoxicillin-clavulanic, respectively. Additionally, more than 85 % of penicillin-allergic patients can tolerate cephalosporins with different R^1 side chains, decreasing to 65 % if the side chain is identical. It is known that third and fourth generation cephalosporins are well tolerated by penicillin-allergic patients, probably because their chemical structures differ more from penicillins that those from the first generation. In patients with IgE-mediated allergic reactions to cephalosporins, penicillins can be an alternative treatment in up to

75 % of cases. Moreover, 40 % of patients primarily sensitized to a given cephalosporin also react to others, which might be because some cephaloporins have the same (ceftriaxone and cefotaxime) or very similar (ceftriaxone and cefuroxime) side chain structures. Finally, carbapenems and monobactams are good alternative for patients with penicillin and/or cephalosporin allergy because cross-reactivity occurs in <1 % of these cases. For all betalactams, tolerance is higher in T-cell-mediated reactions than IgE-mediated. These results show that alternative treatments for infectious disease are available to patients with allergic reactions to betalactams, from within the same group of antibiotics. Nevertheless, this general rules need to be analyzed patient by patient, and skin tests and graded challenge with the betalactam that is going to be administered are recommended.

Keypoints

- Patients with IgE- or T-cell-mediated allergy to betalactams can have selective reactions, specific to one betalactam with good tolerance to others, or be cross-reactive, recognizing several different chemically related betalactams.
- The percentage of selective reactions to the different betalactam compounds is higher than previously reported and patients should be studied in order to increase the treatment options available.

Introduction

Drug reactions with an immunological basis or allergic drug reactions account for 6–10 % of all adverse drug reactions [1]. They can be induced by heterogeneous compounds with very different chemical structures, and one of the most frequent culprits is antibiotics, especially betalactams (BL) [2].

BL allergy is overestimated, and <40 % of the cases initially considered allergic are confirmed [2]. This diagnosis, real or not, led to the use of alternative and more expensive antibiotics with more adverse effects, potentially leading to bacterial resistance and longer hospital stays [3•]. This allergic response, whether IgE- or T-cell-mediated, can be specific to one BL, with the patient having good tolerance to others, or cross-reactive, with the patient reacting to different BLs. From a clinical point of view, the term BL cross-reactivity implicates the possibility of reacting to a BL that is different to the one inducing the primary sensitization, but chemically related.

Immunochemistry

To analyze clinical cross-reactivity, it is necessary to understand the basic aspects of the chemical structures, the degradation pathways, and immunological recognition.

BL chemical structure

BLs have a common four-member BL ring, which provides the antibacterial activity, and are classified into different groups: penicillins, cephalosporins, monobactams, carbapenems, and clavams (Fig. 1). In all except monobactams, the BL ring is condensed to another different ring: in penicillins, a five-member

sulfur ring (thiazolidine); in cephalosporins, a six-member sulfur ring (dihydrothiazine); in carbapenems, a five-member ring (dihydropyrrole); and in

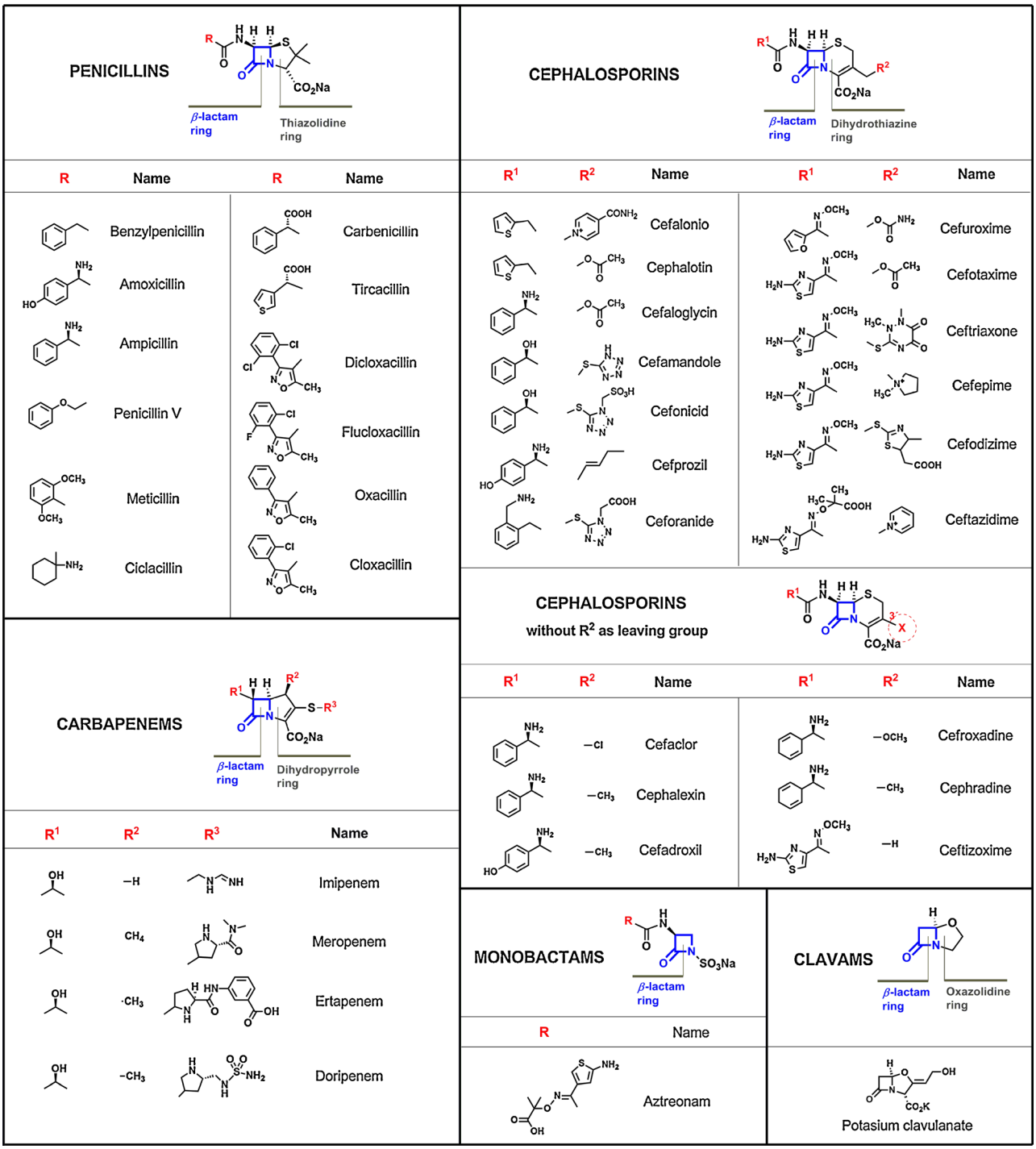

Fig. 1. Chemical structures of different BLs.

clavams, a five-member oxygen ring (oxazolidine). Both fused rings taken together (the bicyclic structure) constitute the core, or nuclear region, of every BL group.

Moreover, all these antibiotics, except clavams, display different R substituents, also called side chains. In all cases, a side chain (R or R^1) is bound to the BL ring, and cephalosporins and carbapenems contain additional side chains (R^2 and/or R^3) associated with the second ring.

BL antigenic determinants

The formation of the antigenic determinants of BLs requires the nucleophilic attack at the BL carbonyl by the amino groups of the protein, leading to the drug–protein adduct (Fig. 2). For benzylpenicillin (BP), a number of products have been described such as the benzylpenicilloyl (BPO), formed after its spontaneous conjugation to proteins and represents 95 % of the antibody recognition [4]. The remaining percentage is formed by structures produced after metabolism (benzylpenicillenate, benzylpenicilloic acid, benzylpenicillanyl, benzylpenamaldate, benzylpenaldate, D-benzylpenicillamine, and benzylpenicilloyl), which have not been fully characterized immunochemically [5]. The production of monoclonal antibodies helped to characterize BP and amoxicillin (AX) antigenic determinants [6, 7], with three different epitopes identified (the side chain, the thiazolidine ring, and the part that results from the conjugation of BL to the protein carrier), although these regions can overlap [7].

Although penicillins and cephalosporins share the BL ring, there are big differences in the determinants they produce after binding to a protein carrier because of their different degradation processes. Cephalosporins undergo fragmentation of the BL and dihydrothiazine rings, and the resultant compounds are extremely unstable with cephalosporoyl adducts degrading through dihydrothiazine ring rupture, with the expulsion of R^2 the substituent, leading to multiple structures that have not been well defined [8, 9]. This unresolved question, as well as whether R^1 and/or R^2 side chains are part of the antigenic determinant, may have important implications for the allergic response. In the majority of clinically relevant cephalosporins, the presence of a good leaving group at the 3′ position (—CH_2—R^2 side chain) increases the reactivity of the BL via the elimination of R^2. However, for other cephalosporins such as cefaclor, ceftizoxime, cefrodaxime, cefadroxil, cephalexin, and cephradine, there is no R^2 group at the 3′ position, but instead a substituent (e.g., chloride, methyl, or methoxy) whose expulsion is not so evident [10]. Regardless of the reactivity of R^2, there is clinical evidence that the R^1 side chain may form part of the antigenic determinant and contribute to IgE induction and cross-reactivity.

Carbapenems differ from penicillins in that their five-member ring is unsaturated and contains a carbon atom instead of sulfur. They form adducts that include a stable dihydropyrrole ring structure leading to a high density of homogeneous epitopes [11].

Monobactams contain a monocyclic BL ring. The only commercially available compound is aztreonam, which has the same side chain as ceftazidime [12].

Finally, for clavams, the only available compound is clavulanic acid (CLV), which is prescribed in combination with AX. Its structure presents an increased chemical reactivity due to its bicyclic structure, which

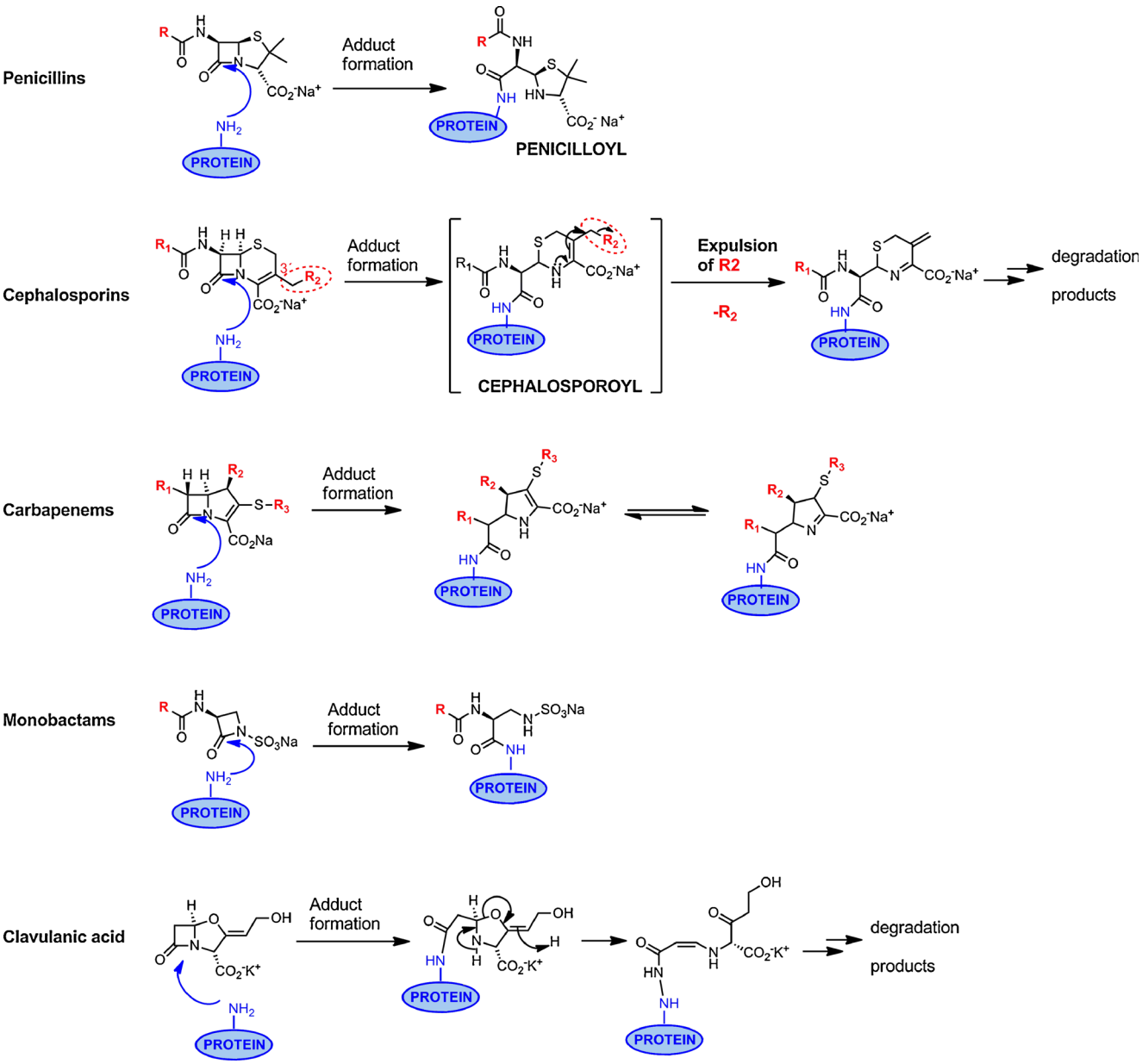

Fig. 2. Conjugation mechanisms for BLs with proteins.

lacks an R side chain substituent in its BL ring, and the presence of an exo-*p*-hydroxyethylidene function at C-2. The resulting adducts show a high instability due to a complex degradation pathways that leads to multiple possible determinants [11].

BL immunological recognition

The antigenic determinants described above can be involved in IgE and T cell allergic reactions, and the details of the immunological

recognition have been more highly studied using penicillins. Early studies from Levine indicated that IgE antibodies to BPO recognize both BP and part of the carrier protein [13]. However, later studies showed that small structures such as the side chain are relevant for recognition, and this has been specifically reported with AX, in an animal model [7] and in humans [14]. Three patterns of IgE response have been described in humans: patients mainly responding to AX and it side chain *p*-hydroxylphenylglycine, patients mainly responding to BP, and patients who recognize BP, AX, and the nuclear part of the BL (6-aminopenicillanic) [14].

This in vitro pattern of recognition correlates with the clinical response: to AX alone (selective reactions) or to both BP and AX (cross-reacting responders). However, selective and cross-reacting are clinical concepts, and although in vitro tests can help, they are not always able to predict the response, in most cases overestimating cross-reactivity [5]. In fact, some degree of IgE recognition to BP has been found in immunoassays and basophil activation test (BAT) in patients with selective reaction to AX and good clinical tolerance to BP [5, 9, 15, 16]. As with IgE-mediated reactions, T-cell-mediated responses to aminopenicillins involve recognition of both the core structure of the BL and the whole molecule (core structure plus side chain) by T cells [17]. However, this recognition often does not correlate with the clinical response, which is in most cases selective.

Although we are far from a full understanding of cephalosporin antigenic determinants, considerable advances have been made in the precise design of well-characterized structures hypothesized to be responsible of the IgE allergic response. One study analyzed synthetic structures consisting of the R^1 side chain bound to the open BL with a small fragment of the dihydrothiazine ring, without the R^2 side chain. They confirmed the cross-reactivity among cephalosporins with the same (ceftriaxone, cefotaxime, and ceftazidime) or similar (cefuroxime, cefotaxime, and cephalotine) R^1 side chains [18]. Differences in the immunochemistry patterns have been described for cephalosporins with an amino group in the R^1 side chain, such as cefaclor and cephalexin, due to the intramolecular cyclation of these aminocephalosporins [19]. On the other hand, cross-reactivity due to similarities in R^2 has not been studied extensively [5], with results having certain degree of speculation, and unable to confirm R^2 as the epitope.

Less information is available for other BL. Carbapenems are able to induce the formation of specific IgG antibodies in animal models and specific IgE in exposed subjects, leading to allergic reactions [11]. Furthermore, aztreonam has been proven to be immunogenic, inducing IgG antibodies [12], and studies using monoclonal antibodies [20] revealed the importance of the side chain as they could recognize aztreonam and ceftazidime. Considering CLV, initial studies indicated a very low immunogenicity [11], although in the last decade, selective IgE-mediated reactions to this compound have been reported by BAT [21, 22••].

Alternative treatments

The increasing prevalence of bacterial resistance and the limited number of antibiotics available makes the assessment of BL cross-reactivity and the use of

alternative treatments crucial for the management of infectious diseases. However, this is not an easy task due to the limited value of skin and in vitro tests, often because the degradation components have not been identified and commercialized diagnostic reagents are only available for few BLs [23]. Moreover, in vitro tests may overestimate clinical cross-reactivity and are not able to rule out the presence of coexisting antibodies with different specificities [14, 24]. Additionally, the time interval between the reaction and the study influences the sensitivity of the test, especially for selective IgE-mediated reactions [25, 26•].

The main goal for studying cross-reactivity is to determine the tolerance to BL from different or even from the same chemical group in order to find the best alternative. We will now describe clinical studies mainly based on skin tests and gradual challenge, largely focusing on IgE-mediated reactions.

Penicillin as an alternative treatment

In 1990, Blanca et al. [27, 28] described a group of patients who developed severe anaphylactic reactions to AX but had good tolerance to BP. In vitro studies confirmed that these patients had IgE antibodies that preferentially recognized the AX side chain structure [29]. These initial studies changed the paradigm that patients with hypersensitivity reactions to any particular penicillin should avoid penicillins altogether. Moreover, it was demonstrated that this response did not change even after repeated doses of BP and penicillin V treatment [30]. This observation, performed in a limited number of patients, was later confirmed in a larger population including 290 patients with proven IgE-mediated hypersensitivity reactions to penicillins [31]. This study demonstrated the importance of selective responses to AX (57.9 %) compared to cross-reactions to BLs (42.1 %) [31]. The number of cross-reactions to BP seems to be decreasing. In fact, in a recent study performed in 55 patients from the same population with IgE-mediated hypersensitivity reactions to AX-CLV, 9 % were cross-reactors to BP, whereas 62 and 29 % were selective reactors to AX and CLV, respectively [22••]. These changes in cross-reactivity likely reflect differences in the pattern of BL consumption. Additionally, in T-cell-mediated reactions to AX, the percentage of selective reactions to this BL is even higher [32, 33], and recent work suggests that it is unnecessary to perform skin testing with BP determinants in their evaluation [34].

It seems that the possibility of inducing selective responses is lower with other penicillins. A recent study of 48 Italian subjects with IgE-mediated allergic reactions to ampicillin found that only three (6.25 %) cases were selective reactors [35]. IgE allergic selective reactions to penicillin V [36–38], cloxacillin [39, 40], and piperacillin [41, 42] have also been reported for a limited number of cases. In T-cell-mediated reactions, it is worth mentioning that selective reactions to piperacillin have been described in patients with cystic fibrosis [43, 44] and as an occupational allergy [45].

Taken together, these results indicate that it is important to explore whether patients that are allergic to one penicillin can tolerate others. This has been confirmed for children [46•] and is now included in European guidelines [47].

Penicillin can also be a safe alternative in patients with allergic reactions to cephalosporins as these responses can be selective, although penicillin cross-reactivity can sometimes occur. The percentage of patients with IgE-mediated allergic reactions to cephalosporins that tolerate penicillin ranges from 50 to 90 %,

differences that may be related to the culprit cephalosporin [48–51]. Tolerance to penicillin is lower with first-generation cephalosporins, probably due to the similarity in the R^1 side chain chemical structure. A recent prospective study performed in 98 subjects with IgE-mediated allergic reactions to cephalosporins and skin test positive confirmed that only 25.5 % had cross-reactivity with penicillins. The risk of cross-reaction with penicillin increase threefold if the culprit cephalosporin has the same or similar side chain at the R^1 position. However, others factors must be involved, since more than 50 % of cross-reactive cases responded to penicillins and cephalosporins with different side chain structures [52]. In another study including ten patients with confirmed IgE-mediated allergy to cefazolin, cross-reactivity with penicillin was only detected in 10 % of cases [51]. In children, similar figures of cross-reactivity have been found, ranging from 0.3 to 23.9 %, with the figure being higher for earlier generation cephalosporins [53].

Given that a large percentage of selective responses in penicillin-allergic patients are due to the side chain structure of AX, BP can be a safe alternative in up to 55 % of patients with IgE-mediated allergic reactions to AX and 90 % to AX-CLV. Moreover, nearly 30 % of cases with reactions to AX-CLV tolerate AX. In patients with IgE-mediated allergic reactions to cephalosporins, penicillins can be an alternative of treatment in up to 75 % of cases. Tolerance in T-cell reactions is even higher.

Cephalosporin as an alternative treatment

Cephalosporins cross-reactivity has been mainly evaluated in patients originally allergic to penicillins. Soon after cephalotin commercialization, anaphylactic reactions in patients with a history of penicillin allergy were reported [54]. The initial incidence of penicillin and cephalosporin cross-reactivity was overestimated at nearly 50 % due to contamination of cephalosporins with penicillin traces [55]. However, this percentage has gradually decreased to 12 % since the 1980s [8, 15, 56–59]. These studies also highlight the importance of the side-chain chemical structure for predicting cross-reactivity. Initial studies indicated that IgE recognizing BP cross-react with some cephalosporins, such as cephalotin and cephaloridine, which contain a similar side chain to BP, but poorly with cefuroxime and cefotaxime, which have very different side chains. In fact, cross-reactivity of penicilllins with cephamandole and cephaloridine was reported in only 10 % of cases [15], increasing to nearly 40 % for AX and cefadroxil, which have identical R^1 side chains [9]. Similar results were detected between ampicillin and cephalexin, which also share the same R^1 side chain [57]. A recent prospective study performed in a large number of patients confirmed these results, finding cross-reactivity in 10.9 % of cases [8]. This increased to 38 % in those with selective reactions to AX receiving cefadroxil [59]. Finally, a meta-analysis has confirmed a significant increase in allergic reactions to first-generation cephalosporins plus cefamandole [odd's ration (OR)=4.8; 95% confidence interval (95 %CI)=3.7 to 6.2] but no increase with second (OR=1.1; 95 %CI=0.6–2.1) or third-generation cephalosporins (OR=0.5; 95 %CI=0.2–1.1) [60].

Data obtained from numerous studies have established different percentages of cephalosporin cross-reactivity in penicilllin-allergic patients depending on penicillin skin test results. This was 3.5–6 % in patients with positive versus 0.6–0.7 % in those with negative penicillin skin test results [15, 56, 57, 61]. This indicated a greater risk of an adverse drug reaction to cephalosporin in patients

with a history of penicillin allergy and a positive penicillin skin test. On the other hand, the role of skin testing for determining cross-reactivity has not been established: It is generally agreed that a positive cephalosporin skin test in penicillin allergic patients indicates cross-reactivity, but disagreement as to whether a negative cephalosporin skin test indicates good tolerance. While some studies have found that all patients with confirmed IgE-mediated allergy to penicillin and negative skin test results with cephalosporins tolerate the administration of the latter [8], others have found that some patients with IgE-mediated selective reactions to AX and negative skin tests to cefadroxil cannot tolerate this cephalosporin [59].

Cross-reactivity is quite rare for T-cell-mediated reactions to penicillins. It has been shown that 97.2 % of 71 patients with T-cell-mediated allergy to aminopenicillins tolerate cephalosporins without an aminobenzyl side chain such as cefpodoxime or cefixime and 71.8 % also tolerate penicillin V, confirming that most are selective reactors [62].

In patients with IgE-mediated allergic reactions to cephalosporins and good tolerance to penicillins, there are two main groups: those only reacting to the culprit cephalosporin and those reacting to more than one cephalosporin. The percentage of patients reacting to one cephalosporin ranges from 57.7 to 63.2 % and the percentage of those reacting to more than one from 36.8 to 42.3 % [48, 50]. The different percentages are probably due to the cephalosporin generation involved in the reaction (selective responders) and similarities in side chain structures (cross-reactors). Taken together, these results indicate that cephalosporins are a safe option for patients with IgE-mediated allergy to penicillins, with 90 % of cases tolerating their administration, decreasing to 60 % when the R^1 side chain is identical to the initial culprit. They may also be a safe option for more than 50 % of patients with IgE-mediated allergy to cephalosporins, with the R^1 side chain structure being critical for predicting tolerance, although other factors appear to be involved.

Carbapenem as an alternative treatment

The incidence of carbapenem hypersensitivity is lower than 3 % [63]. The similarity in the chemical structure between penicillins and carbapenems suggests that great cross-reactivity could exist. Indeed, an early study showed that 25.6 % of penicillin-allergic patients and 47 % of those with positive penicillin skin tests had cross-reactivity with imipenem [64]. Therefore, it was initially recommended to adopt similar precautions as with penicillin when administering imipenem to penicillin-allergic patients, especially in those with positive skin tests.

However, later retrospective studies indicated that cross-reactivity was lower than initially thought, ranging from 9.2 to 11 % [63, 65, 66]. One of these [65]analyzed the medical records of 63 bone marrow transplant recipients with fever and neutropenia, and only 9.5 % developed imipenem allergy, less than for those with well-documented allergies (33 %). Other studies [63, 66] showed that the rate of carbapenem hypersensitivity was higher in those with previous penicillin allergy (ranging from 9.2 to 11 %) than in those without penicillin allergy (ranging from 2.7 to 3.9 %). It has recently been stated that patients considered allergic to penicillins are no more likely to have a reaction to carbapenem than those who were not considered allergic [67].

In the last 10 years, there has been a great interest in the elucidation of the rate of carbapenems cross-reactivity in patients with allergic reactions to penicillins. A number of prospective studies [52, 68–72, 73•, 74], most coming from the same group, have been published for adults and children with IgE-mediated allergic reactions to penicillins or to cephalosporins. Two studies evaluated patients with IgE-mediated hypersensitivity to penicillin and positive skin tests and found that 0.9 % were skin test positive to imipenem [68, 69] or meropenem [68, 69], with all skin test negative cases tolerating their administration. These results have been recently confirmed with imipenem, meropenem, and etarpenem [70]. Similar studies performed in children [71, 72] had equivalent results detecting a cross-reactivity of 0.9 % with meropenem and 0.8 % with imipenem. These low rates are likely to be due to the majority of IgE antibodies from penicillin-allergic patients recognizing specific penicillin determinants and not the shared common nuclear BL [70].

Carbapenems cross-reactivity has also been evaluated in patients with IgE-mediated hypersensitivity reactions to cephalosporins. In a prospective study [52] of 98 patients with IgE-mediated reactions and a positive skin test to cephalosporins, the rate of cross-reactivity to imipenem/cilastatin and meropenem was 1 %. A systematic review [73•] including published data on children and adults who received carbapenem indicated that cross-reactivity was lower in those with penicillin allergy (2.4 %) than in those with cephalosporin allergy (10 %), differences that could be explained by the low number of patients included in the cephalosporin group.

Regarding T-cell-mediated hypersensitivity, animal models have detected very low cross-reactivity between imipinem and other BLs [75]. Studies carried out in humans [74] found a rate of cross-reactivity between different BLs and imipenem of 5.5 %, which was higher than for IgE-mediated reactions. However, these results could not be reproduced in a large series of patients, where absence of cross-reactivity was detected [76].

These studies indicate that carbapenems can be a safe alternative in more than 99 % of patients with either IgE- or T-cell-mediated reactions to penicillins or cephalosporins.

Aztreonam as an alternative treatment

Aztreonam is generally well tolerated, only causing allergic reactions in 2.1 % of cases, and only 0.2 % are IgE-mediated [77]. Initial studies in experimental animals [12] and humans [78, 79] showed that aztreonam has a negligible cross-reactivity with penicillins [78, 79]. This has been later confirmed in various prospective studies [70, 80–82]. The most recent study found that all penicillin-allergic patients with negative skin tests to aztreonam tolerated their administration with escalating doses [70]. Similar results have been published in patients with delayed reactions to penicillins [83].

It is important to mention that cross-reactivity of aztreonam seems to be higher in patients with cystic fibrosis, probably reflecting repeated administration. In fact, in a study performed by Moss [84] on cystic fibrosis patients, 6.2 % of cases with allergy to semisynthetic penicillins had a positive skin test result to aztreonam.

Cross-reactivity between cephalosporins and aztreonam can be higher in those sharing the same side chain, as occurs with ceftazidime [85]. In a recent prospective study [52] performed in patients with IgE-mediated allergic reactions to cephalosporin and who were skin test positive, 3.06 % of cases (three patients) had positive skin tests to aztreonam (one was positive to all BL determinants tested, the other to ceftazidime, and the third to cefodizime).

These results indicate that aztreonam is a safe alternative for patients with IgE- and/or T-cell mediated penicillin allergy and for patients who are allergic to cephalosporins with different side chains.

To conclude, contrary to what was previously thought, it is clear that some BLs can be an option of treatment for patients allergic to other BLs. This is particularly the case for patients with T-cell-mediated reactions. However, chemical structure must be taken into account when selecting an alternative. Treatment options must be analyzed patient by patient, and a skin test for any BL that is going to be administered, followed by a graded challenge, is recommended.

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Compliance with Ethics Guidelines

Conflict of Interest

María Isabel Montañez declares that she has no conflict of interest. Adriana Ariza declares that she has no conflict of interest. Cristobalina Mayorga declares that she has no conflict of interest. Tahia Diana Fernandez declares that she has no conflict of interest. María José Torres declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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This is one of the few studies showing selective reactions to clavulanic acid. This article found that almost a third of amoxicillin-clavulanic allergic patients had good tolerance to benzylpenicillin and amoxicillin but were selective responders to clavulanic acid.

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