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Cross-Reactivity among Beta-Lactams

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Abstract Penicillins and cephalosporins are the major classes of beta-lactam (BL) antibiotics in use today and one of the most frequent causes of hypersensitivity reactions to drugs. Monobactams, carbapenems, oxacephems, and beta-lactamase inhibitors constitute the four minor classes of BLs. This review takes into account mainly the prospective studies which evaluated cross-reactivity among BLs in subjects with a well-demonstrated hypersensitivity to a certain class of BLs by performing allergy tests with alternative BLs and, in case of negative results, administering them. In subjects with either IgE-mediated or T-cell-mediated hypersensitivity, cross-reactivity among BLs, particularly among penicillins and among cephalosporins, as well as between penicillins and cephalosporins, seems to be mainly related to structural similarities among their side-chain determinants. Specifically, in penicillin-allergic subjects, cross-reactivity between penicillins and cephalosporins may exceed 30 % when they are administered cephalosporins with identical side chains to those of responsible penicillins. In these subjects, a few prospective studies have demonstrated a rate of cross-reactivity between penicillins and both carbapenems and aztreonam lower than 1 %. With regard to subjects with an IgE-mediated hypersensitivity to cephalosporins, in a single study, about 25 % of the 98 subjects with such hypersensitivity had positive results to penicillins, 3 % to aztreonam, 2 % to imipenem/cilastatin, and 1 % to meropenem. The cross-reactivity related to the selective recognition of the BL ring by IgE or T lymphocytes, which entails positive responses to all BLs tested, appears to be exceptional. Some studies concerning cross-reactivity among BLs have found patterns of allergy-test positivity which cannot be explained by either the common BL ring or by similar or identical side chains, thus indicating the possibility of coexisting sensitivities to different BLs because of prior exposures to them.

Keywords Beta-lactams · Cross-reactivity · Hypersensitivity · Aztreonam · Carbapenems · Cephalosporins · Penicillins

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Introduction

Beta-lactam (BL) antibiotics are classified into two major classes, penicillins and cephalosporins, and four minor ones, carbapenems, monobactams, oxacephems, and beta-lactamase inhibitors (i.e., clavulanic acid, sulbactam, and tazobactam). The basic structure of all BLs consists of a four-membered BL ring. In penicillins, it is attached to a five-membered thiazolidine ring; the side chain (R) distinguishes the different penicillins (Fig. 1). Instead of the five-membered thiazolidine ring of penicillins, cephalosporins have a six-membered sulfur-containing dihydrothiazine ring and two side chains (R1 and R2), which distinguish the different compounds (Fig. 2). Carbapenems (e.g., imipenem, meropenem, ertapenem, and doripenem) contain a carbon double bond instead of

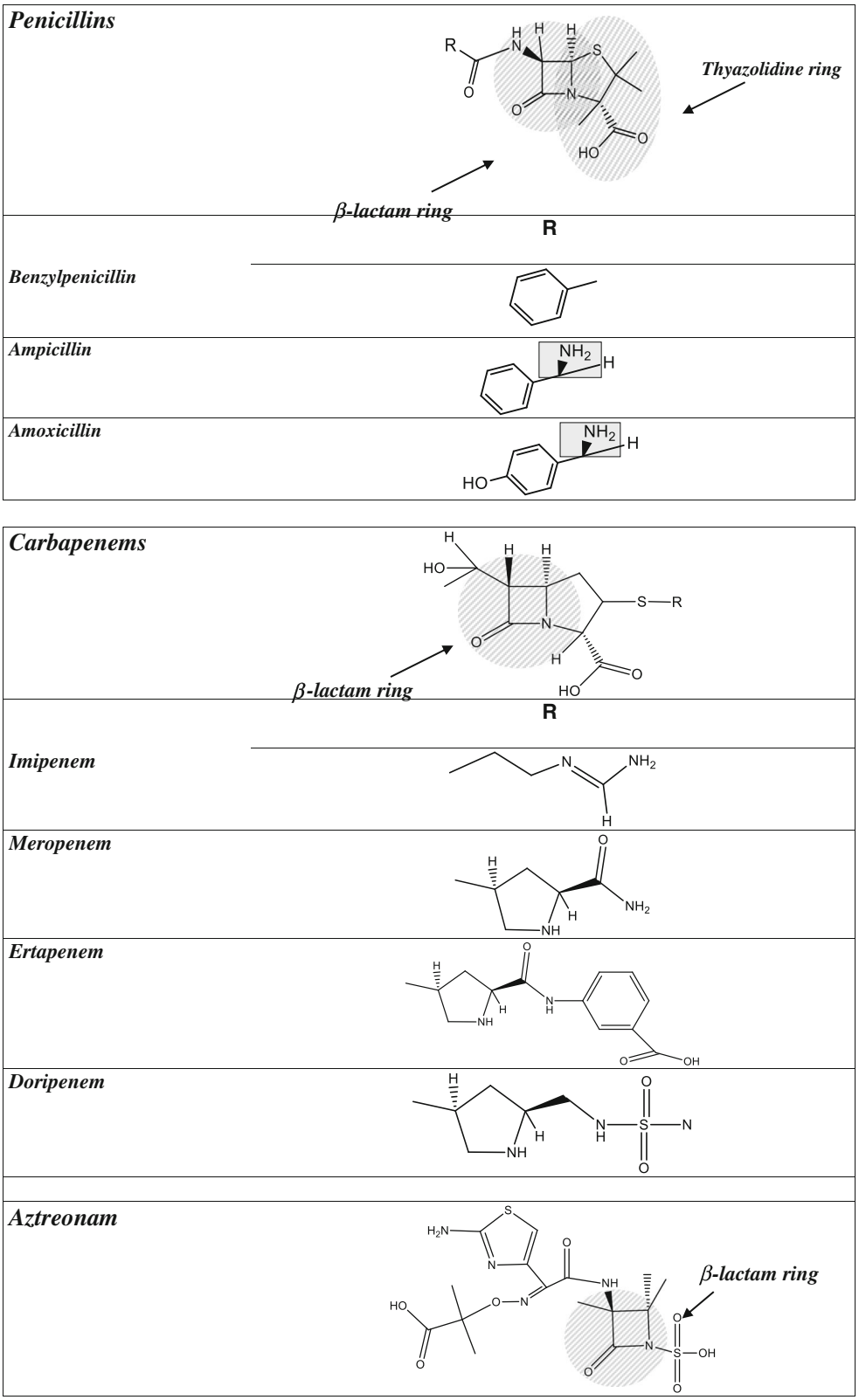

Fig. 1 Chemical structures of penicillins, aztreonam, and carbapenems, with the amino group of ampicillin and amoxicillin highlighted in *gray*

sulfur in the five-membered thiazolidine ring and have a side chain (R), which distinguishes the different carbapenems (Fig. 1). Aztreonam is the only monobactam antibiotic commercially available; it contains the BL ring without an attached five- or six-membered sulfur ring (Fig. 1).

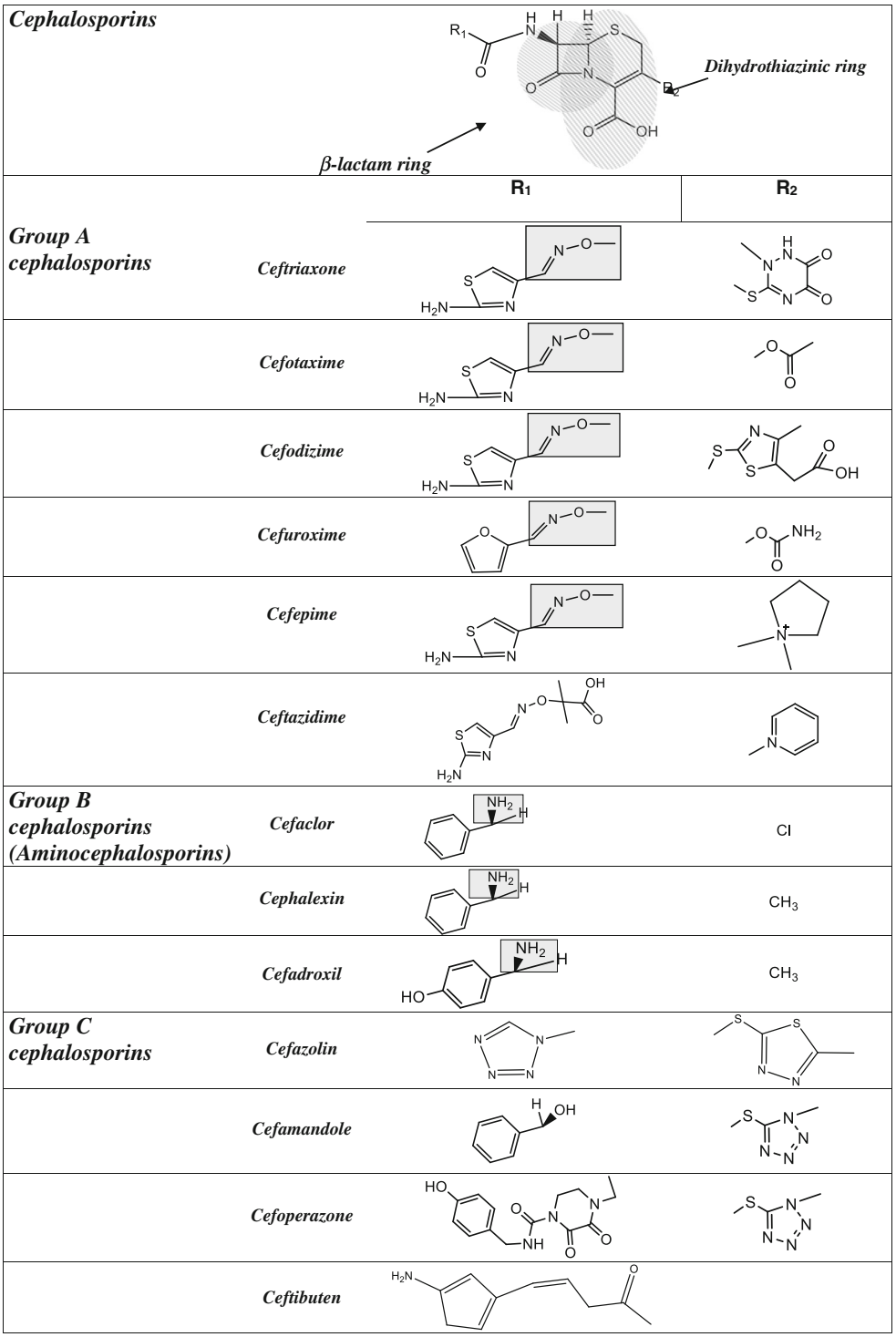

Fig. 2 Chemical structures of cephalosporins, with the methoxyimino group of cephalosporins of group A and the amino group of cephalosporins of group B highlighted in *gray*

The BL ring, the thiazolidine/dihydrothiazine rings, and the side groups are all potentially immunogenic. In particular, side chains are important sites of immunological recognition and therefore may cause allergic cross-reactivity [1, 2••, 3].

BLs constitute one of the most frequent causes of both IgE-mediated and T-cell-mediated hypersensitivity reactions to drugs [1]. The former usually occur within 1 h after the last drug administration (i.e., immediate reactions), while the latter appear more than 1 h after the last drug administration (i.e., nonimmediate reactions) [4].

This review takes into account mainly the prospective studies which evaluated cross-reactivity among BLs in subjects

with a well-demonstrated IgE-mediated or T-cell-mediated hypersensitivity to a certain class of BLs by performing allergy tests with alternative BLs and, in case of negative results, administering them. The great majority of the studies of this review concerning subjects with an IgE-mediated hypersensitivity to penicillins and/or cephalosporins have been performed in Europe [1, 2••, 3–25, 26••, 27, 28•, 29•, 30••]. In these studies [1, 2••, 3–25, 26••, 27, 28•, 29•, 30••], most participants reported anaphylactic reactions. This phenotype appears to be much less frequent in US studies [31, 32•]. This is likely due to differences in the populations assessed, including those related to genetic factors, and in the methodology used. For example, the aforesaid European studies [1, 2••, 3–25, 26••, 27, 28•, 29•, 30••] included only subjects who had experienced immediate reactions, such as anaphylactic or urticarial/angioedematous ones, whereas the US studies [31] included subjects with histories not only of anaphylaxis or hives but also of other types of rashes, local swelling at the site of injection, respiratory problems, and gastrointestinal or unknown symptoms. With regard to the genetic factors, a recent study by Guéant et al. [33], performed in two populations from Spain and Italy, demonstrated that IgE-mediated hypersensitivity to BLs, especially penicillins, results from complex gene-environment interactions in which genetic susceptibility of HLA type 2 antigen presentation plays a central role.

Cross-Reactivity among Penicillins

As far as IgE-mediated hypersensitivity to penicillins is concerned, literature data indicate a high degree of cross-reactivity among semi-synthetic penicillins, especially aminopenicillins (i.e., amoxicillin, ampicillin, bacampicillin, and pivampicillin) which share an amino group in their side chain (Fig. 1), as well as between semi-synthetic penicillins and benzylpenicillin (penicillin G), mainly on the basis of clinical histories and positive responses to skin tests and serum-specific IgE assays [13, 14, 16, 18–20, 25, 28•]. In particular, in some studies [13, 14, 16, 18–20, 28•], subjects who had reacted to semi-synthetic penicillins, such as aminopenicillins, piperacillin, and cloxacillin, displayed positive responses to skin tests with semi-synthetic penicillins other than those responsible and/or with the classic benzylpenicillin reagents: penicilloyl-polylysine (PPL) and/or minor determinant mixture (MDM). Specifically, a study by Torres et al. [13] diagnosed an immediate hypersensitivity to penicillins in 290 subjects by using skin tests, specific IgE assays, and challenges. One hundred and sixty-eight subjects (57.9 %) were positive to benzylpenicillin determinants and were classified as non-selective responders, while 122 patients (42.1 %) were positive to amoxicillin and/or ampicillin, negative to benzylpenicillin reagents, tolerated benzylpenicillin graded challenges, and were classified as selective responders. Recently, Blanca-Lopez et al. [29•] diagnosed, by skin tests or challenges, a hypersensitivity in 58 (21.6 %) of 268 subjects with histories of immediate reactions to amoxicillin or amoxicillin + clavulanic acid. Seven of these 58 subjects were positive to benzylpenicillin determinants. Of the remaining 51 cases, 40 (78 %) were classified as selective responders to amoxicillin, with good tolerance of benzylpenicillin and penicillin V, and 11 (22 %) were classified as selective responders to clavulanic acid, with good tolerance of benzylpenicillin, penicillin V, and amoxicillin.

With regard to cross-reactivity among penicillins in subjects with a T-cell-mediated hypersensitivity to these BLs, a study of ours [34] diagnosed such hypersensitivity in 157 adults with histories of nonimmediate reactions to penicillins, mostly aminopenicillins, on the basis of positive responses to patch tests and/or delayed-reading intradermal tests. All were positive to the responsible penicillins. About 60 % of these subjects were negative to PPL, MDM, and benzylpenicillin; however, they did not undergo benzylpenicillin challenges.

In a previous study of ours [35], 33 of the 60 subjects reporting maculopapular rashes during aminopenicillin treatments were positive to delayed-reading intradermal tests and patch tests with ampicillin and amoxicillin and three also with benzylpenicillin; 17 subjects negative to benzylpenicillin reagents underwent challenges with penicillin V and tolerated them.

Cross-Reactivity between Penicillins and Cephalosporins

The clinical importance of cross-reactivity between penicillins and cephalosporins is demonstrated by a study by Pumphrey and Davis [36], who found that six of 12 fatal anaphylactic reactions to antibiotics were provoked by the first dose of a cephalosporin treatment; three of the six patients were allergic to amoxicillin and one to benzylpenicillin.

Cross-reactivity between benzylpenicillin and first- and early (introduced before 1980) second-generation cephalosporins has been reported to occur in up to 10 %, and for third generation ones in 2–3 %, of penicillin-allergic patients [37]. However, the contamination of these early cephalosporins with trace amounts of benzylpenicillin may have entailed an overestimation of the degree of cross-reactivity between these BLs.

A meta-analysis of studies performed between 1966 and 2005, which compared hypersensitivity reactions to cephalosporins in penicillin-allergic and non-penicillin-allergic patients, reported a significant increase (odds ratio = 4.8) in allergic reactions to all first-generation cephalosporins, such as cephalothin, cephaloridine, and cephalexin, plus cefamandole, but no increase with second- or third-generation cephalosporins [38].

Studies performed since 1990 on samples of at least 30 subjects with a documented IgE-mediated hypersensitivity to penicillins [7, 12, 14, 24] have demonstrated a rate of positive responses to skin tests with cephalosporins ranging from 0 % (0 of 41 subjects) [12] to 14.7 % (5 of 34) [7]. Specifically, the highest rate of positive responses to skin tests was observed in the study by Audicana et al. [7], in which 5 of 34 penicillin-allergic patients were positive to cephalexin.

More recently, Liu et al. [39] assessed cross-reactivity with cephalosporins in 294 subjects with histories of penicillin allergy and positive penicillin skin tests by performing serum-specific IgE assays with four penicillins (benzylpenicillin, penicillin V, ampicillin, and amoxicillin) and seven cephalosporins (cephalexin, cephalothin, cefazolin, cefoperazone, ceftriaxone, ceftazidime, and cefotaxime). Sixty-six subjects (22.4 %) were positive to cephalosporins; the highest rate (7.3 %) of positivity was to cefoperazone, whereas the lowest (2.6 %) was to ceftriaxone.

In some of the aforesaid studies [7, 12, 14, 24], penicillin-allergic participants displaying negative results to skin tests with cephalosporins, such as cephalexin, cefazolin, cefuroxime, ceftazidime, and ceftriaxone, underwent challenges with the cephalosporins concerned. Of a total of 240 subjects, only two in the study by Caimmi et al. [24] reacted (to cefuroxime), while the remaining 238 subjects tolerated cephalosporin challenges (Table 1). However, it should be noted that a study by Yoon et al. [40] found a rate of 5 % of false positivities to cephalosporin skin tests. In other studies [5, 8, 9, 41], penicillin-allergic patients underwent challenges with cephalosporins, such as cefamandole, cephalexin, cefadroxil, and ceftriaxone, without undergoing skin tests with the cephalosporin concerned. The highest rate of positive challenges (38 %) was observed in the study by Miranda et al. [9], who administered cefadroxil to 21 subjects allergic to amoxicillin.

Literature data indicate that cross-reactivity as a result of antibody recognition seems to be more closely related to side chain similarity or identity than to the central BL ring, although shared epitopes from other parts of the molecule also account for cross-reactivity [42, 43]. In effect, cephalothin and cefamandole have side-chain structures similar to those of penicillins. Specifically, cefamandole, benzylpenicillin, and ampicillin have similar side-chain structures, which are benzyl derivatives [44]. In addition, ampicillin and cephalexin share an identical side chain with an amino group, as do amoxicillin and cefadroxil (Figs. 1 and 2).

In penicillin-allergic patients, however, positive responses to allergy tests with cephalosporins do not appear to be related only to side chains. In the aforesaid study of ours [14], cross-reactivity and tolerability of cephalosporins were assessed in 128 patients with histories of immediate reactions to penicillins and positive skin tests to at least one penicillin reagent. The allergy workup included skin tests with both penicillin and cephalosporin reagents, as well as serum-specific IgE assays. Subjects presenting negative results to ceftazidime, cefotaxime, cefuroxime, and ceftriaxone underwent challenges with the latter two cephalosporins. Fourteen patients displayed positive skin tests to cephalosporins. Nine subjects were positive to cephalothin and/or cefamandole (Table 2, patients no. 1, 2, 6, and 9–14), whereas one subject, probably with IgE antibodies against the BL ring, was positive to all the reagents tested (Table 2, patient no. 3). The remaining four patients displayed different patterns of positivity to cephalosporins, which cannot be explained by the fact that penicillins and cephalosporins share either the common BL ring or similar or identical side chains (Table 2, patients no. 4, 5, 7, and 8). In these cases, therefore, coexisting sensitivities because of prior exposures may be possible. Considering all this, it could be risky to treat penicillin-allergic patients even with cephalosporins selected on the basis of side-chain differences. For this reason, pre-treatment skin tests with the cephalosporins concerned are advisable before their administration to penicillin-allergic patients [14].

With regard to T-cell-mediated hypersensitivity to penicillins, six studies assessed cross-reactivity with cephalosporins in a total of 454 adults with such hypersensitivity by performing delayed-reading skin tests and/or patch tests with cephalosporins, and in case of negative results, challenges [45–49, 50••] (Table 3). In these studies, the rate of positive

Table 1 Rate of cephalosporin positive challenges in penicillin-allergic patients with negative skin tests with the cephalosporin concerned

	No. of subjects	Challenges		
		Administered drug(s)	Administered route(s)	No. of reactions (%)
Audicana et al. [7]	29	CH, CZ	CH: Oral, CZ: IV	0
Novalbos et al. [12]	41	CA, CU, CT	IM	0
Romano et al. [14]	101	CU, CT	CU: Oral, CT: IM	0
Caimmi et al. [24]	69	CU	Oral	2
Total	240			2

CA cefazolin, *CH* cephalexin, *CT* ceftriaxone, *CU* cefuroxime, *CZ* ceftazidime, *IM* intramuscularly, *IV* intravenously

Table 2 Clinical characteristics and patterns of reactivity of the 14 patients of the study by Romano et al. [14] with skin-test positivity to cephalosporins

Pt. No.	Culprit drug	Type of reaction	Skin tests												IgE assays			
			PPL	MDM	PG	AM	AX	PP	CL	CM	CU	CZ	CT	CX	PG	PV	AM	AX
1	AM	UA	+	+	−	−	+	−	+	−	−	−	−	−	−	−	−	−
2	PG	An	+	+	+	+	+	−	+	+	−	−	−	−	+	+	+	+
3	AX	An	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4	AX	An	−	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−
5	AM/AX	U/An	+	−	−	−	−	−	−	−	−	−	+	−	+	+	+	+
6	AM	An	−	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−
7	AX	U	−	−	−	+	+	−	−	−	−	−	−	+	−	−	−	−
8	AX	U	+	+	−	−	−	−	+	+	+	−	+	−	+	+	+	+
9	AX	An	−	+	+	+	+	+	+	+	−	−	−	−	−	+	−	−
10	PG	UA	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−
11	BC	An	−	+	+	+	+	−	−	+	−	−	−	−	−	−	−	−
12	AX	An	−	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−
13	AX	An	−	−	−	−	+	+	+	−	−	−	−	−	−	−	−	−
14	AX	An	+	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−

AM ampicillin, *An* anaphylaxis, *AX* amoxicillin, *BC* bacampicillin, *CL* cephalothin, *CM* cefamandole, *CT* ceftriaxone, *CU* cefuroxime, *CZ* ceftazidime, *CX* cefotaxime, *MDM* minor determinant mixture, *PG* penicillin G, *PPL* penicilloyl-polylysine, *PV* penicillin V, *U* urticaria, *UA* urticaria and angioedema

responses to cephalosporin allergy tests ranged from 2.8 [48] to 31.2 % [46]. Specifically, in the study by Trcka et al. [48], two of the 71 patients with delayed hypersensitivity to aminopenicillins and negative patch tests with cefpodoxime and cefixime, who underwent challenges with these cephalosporins, developed an exanthema with cefpodoxime and cefixime, respectively. In the study by Phillips et al. [46], five of the 16 subjects with a T-cell-mediated hypersensitivity to ampicillin were patch test positive to cephalexin. Of the 11 subjects with negative patch tests, six underwent oral challenges with either cephalexin or cefaclor and tolerated them. In the study by Buonomo et al. [49], which is the largest of the three studies performed by the same group [45, 47, 49], 17 of the 97 patients evaluated had positive patch tests to at least one of the six cephalosporins tested (Table 3). Overall, this study found a rate of positive responses to allergy tests with aminocephalosporins of 18.5 % (18 of 97 participants): 15 were patch test positive to at least one aminocephalosporin. Of the 82 negative subjects, 37 underwent challenges with cephalexin, and four reacted; one of the latter was patch test positive to cefaclor. All challenges performed with cefixime, ceftibuten, cefuroxime, and ceftriaxone in subjects with negative patch tests with these cephalosporins were tolerated. In a recent study of ours [50••], 214 consecutive adults with nonimmediate reactions to penicillins and positive delayed-reading skin tests to at least one penicillin reagent underwent skin tests with cephalexin, cefaclor, cefadroxil, cefuroxime, and ceftriaxone. Most participants had experienced maculopapular exanthemas, whereas five had a toxic epidermal necrolysis (TEN) and three had an acute generalized exanthematous pustulosis (AGEP). Subjects with negative results were challenged with the cephalosporins concerned. All subjects displayed negative skin tests to cefuroxime and ceftriaxone and tolerated challenges. Forty (18.7 %) of the 214 subjects displayed positive skin tests to at least one aminocephalosporin (Table 3). Among these 40 participants, there were the three subjects with AGEP and two of the five with TEN. Of the 174 negative subjects, 170 underwent challenges; one reacted to cefaclor.

In the aforesaid studies [45–49, 50••], the positive responses of allergy tests to aminocephalosporins are related to similar or identical side chains, whereas positivities to cephalosporins, such as cefuroxime, cefpodoxime, and cefixime, which have side chains dissimilar from those of penicillins, suggest the possibility of coexisting sensitivities, as in subjects with IgE-mediated hypersensitivity.

Cross-Reactivity between Penicillins and Carbapenems

Penicillins and carbapenems have a structural similarity related to their bicyclic core, composed of a five-membered ring attached to the BL ring (Fig. 1). Until the last decade, it was considered potentially harmful to administer carbapenems to patients with IgE-mediated hypersensitivity to penicillins [51], because in a study by Saxon et al. [52] nine (47.4 %) out of 19 subjects with an IgE-mediated hypersensitivity to

Table 3 Cross-reactivity and tolerability of cephalosporins in subjects with a T-cell-mediated hypersensitivity to penicillins

Author	No. of patients	Responsible penicillins	Tested cephalosporins (methods)	No. of positive patients (%)	No. of positive challenges (%)
Patriarca et al. [45][a]	29	Aminopenicillins, penicillin G, piperacillin	Cephalothin, cephalexin, cefaclor, cefadroxil, cefatrizine, cefamandole, cefuroxime, cefotaxime, ceftriaxone, cefixime, and ceftibuten (skin tests and patch tests)	4 (13.8) [1 to cephalexin, 1 to cefadroxil, 1 to cefuroxime, and 1 to cephalothin, cephalexin, and cefadroxil]	8/125 (6.4) [5 to cephalexin, 1 to cefadroxil, 1 to ceftriaxone, and 1 to cefixime]
Phillips et al. [46]	16	Aminopenicillins	Cephalexin (patch tests)	5 (31.2)	0/6 (0 %)
Schiavino et al. [47][a]	27	Aminopenicillins	Cephalothin, cephalexin, cefaclor, cefadroxil, cefatrizine, cefamandole, cefuroxime, ceftriaxone, cefixime, ceftibuten, and cefotaxime (skin tests and patch tests)	1 (3.7) [to cephalexin]	3/101 (2.9) [to cephalexin]
Trcka et al. [48]	71	Aminopenicillins	Cefpodoxime and cefixime (patch tests)	0 (0)	2/142 (1.4)
Buonomo et al. [49][a]	97	Aminopenicillins, penicillin G, unknown	Cephalexin, cefaclor, cefuroxime, ceftriaxone, cefixime, and ceftibuten (skin tests and patch tests)	17 (17.5) [5 to cephalexin, 4 to cefaclor, 2 to cephalexin and cefaclor, 2 to cefuroxime and cefaclor, 1 to cefuroxime, 1 to cephalexin and cefuroxime, 1 to cefuroxime and cefixime, and 1 to cefaclor, cephalexin, and cefuroxime]	4/218 (1.8 %) [to cephalexin]
Romano et al. [50••][b]	214	Aminopenicillins, penicillin G, piperacillin	Cephalexin, cefaclor, cefadroxil, cefuroxime, and ceftriaxone (skin tests and patch tests)	40 (18.7 %) [16 to cephalexin and cefaclor, 15 to cephalexin, cefaclor, and cefadroxil, 7 to cefaclor, 1 to cefaclor and cefadroxil, and 1 to cefadroxil]	1/935 (0.1) [to cefaclor]

[a] In this study, not all participants underwent skin tests, patch tests, and, in case of negative results, challenges with the entire panel of cephalosporins

[b] In this study, challenges with aminocephalosporins were not performed in subjects who had experienced TEN or AGEP

benzylpenicillin presented positive skin tests to imipenem and/or its metabolites. Subsequent prospective studies of ours—two including only adults [18, 20] and two including only children [21, 23]—performed on samples larger than 100 subjects with a documented IgE-mediated hypersensitivity to penicillins have demonstrated a cross-reactivity rate of approximately 1 % between penicillins and both imipenem and meropenem, on the basis of positive responses to carbapenem skin testing, putting an end to the alarm connected with a significant allergic cross-reactivity between penicillins and carbapenems [53]. Recently, in a study of ours [28•], 212 consecutive adults with immediate reactions to penicillins and positive skin tests to at least one penicillin reagent underwent skin tests with imipenem/cilastatin, meropenem, and ertapenem. All subjects displayed negative skin tests to carbapenems; 211 accepted challenges and tolerated them.

These data indicate the tolerability of carbapenems in penicillin-allergic subjects. In those who especially require these BLs, however, pre-treatment skin tests are advisable, both because rare cases of cross-reactivity have been reported [18, 20] and because negative results indicate tolerability.

As far as T-cell-mediated hypersensitivity to penicillins is concerned, four studies by the same group evaluated cross-reactivity and tolerability of imipenem/cilastatin in subjects with such hypersensitivity [45, 47, 49, 54]. The first two studies [45, 47] did not find any cross-reactivity in a total of 57 subjects, while in the third one [54] four of the 73 subjects evaluated presented positive responses to patch tests with imipenem/cilastatin. In any case, all 64 negative subjects who underwent imipenem/cilastatin challenges tolerated them. However, in a recent study of ours concerning 204 subjects with a T-cell-mediated hypersensitivity to penicillins [55•], all patients displayed negative results to skin tests with imipenem/cilastatin, as well as with meropenem and ertapenem and tolerated challenges with all these carbapenems.

Considering the results of the last study, the positive responses to patch tests with imipenem/cilastatin found in four patients by Schiavino et al. [54] appear quite surprising. In particular, it seems unlikely that all four patients of the aforesaid study [54] positive to imipenem/cilastatin patch tests were negative to delayed-reading intradermal tests, which are more sensitive than patch tests in

evaluating subjects with delayed hypersensitivity to BLs [56]. Moreover, the study by Schiavino et al. [54] found two patch test positivities to PPL. Actually, patients with T-cell-mediated hypersensitivity to penicillins present negative responses to PPL, which are related to the nature of the carrier; in effect, polylysine is a non-immunogenic carrier, as observed by Levine [57] in delayed reactions to penicillins. Therefore, the positive responses to imipenem/cilastatin patch tests may have been cases of false positivities, as were those to PPL.

In a recent study by Buonomo et al. [49], four of 97 subjects with a T-cell-mediated hypersensitivity to penicillins were patch test positive to imipenem/cilastatin; all negative subjects tolerated challenges. However, the authors did not specify if their study also included subjects who had participated in the previous study by their group [54].

Cross-Reactivity between Penicillins and Aztreonam

Four studies evaluated cross-reactivity to aztreonam in samples larger than ten subjects with IgE-mediated hypersensitivity to penicillins by performing allergy tests and challenges with aztreonam [6, 22, 28•, 58]. Two studies [22, 28•] did not find any cross-reactivity in a total of 252 such subjects. Specifically, in the aforesaid study of ours [28•], 212 consecutive adults with a well-demonstrated IgE-mediated hypersensitivity to penicillins displayed negative skin tests to aztreonam; 211 accepted challenges and tolerated them. In the other two studies [6, 58], which evaluated a total of 45 penicillin-allergic subjects, three participants were positive to allergy tests with aztreonam. In the study by Vega et al. [6], two subjects positive to skin tests and serum-specific IgE assays, respectively, underwent aztreonam challenges and tolerated them, while in the study by Moss [58], one (6.2 %) of 16 cystic fibrosis patients allergic to semi-synthetic penicillins was skin test positive to aztreonam and did not undergo a challenge.

With regard to T-cell-mediated hypersensitivity to penicillins, five studies did not find any cross-reactivity with aztreonam in subjects with such hypersensitivity [45, 47, 49, 50••, 59]. Specifically, the largest of these studies [50••] evaluated 214 subjects by performing both patch tests and delayed-reading skin tests with aztreonam. None of these participants displayed positive responses to aztreonam allergy tests; 213 of them accepted aztreonam challenges and tolerated them.

Cross-Reactivity among Cephalosporins

A few studies evaluated subjects with immediate reactions to cephalosporins using serum-specific IgE assays and skin tests with penicillin reagents, as well as with different cephalosporins, including those responsible [10, 11, 15, 17, 27]. Three patterns of reactivity were observed: cross-reactivity with penicillins, selective reactivity to responsible cephalosporins, and cross-reactivity with cephalosporins other than those responsible.

Specifically, in a study by Antunez et al. [17], 24 subjects with an IgE-mediated hypersensitivity to cephalosporins underwent skin tests and RAST with a panel of penicillins and cephalosporins, as well as RAST-inhibition studies. Twenty-one had positive skin tests to cephalosporins: 12 only to the responsible compound and nine to more than one cephalosporin.

RAST and RAST-inhibition studies demonstrated that the side chain at the R1 position is crucial for recognition and cross-reactivity. In effect, five subjects were positive to cefuroxime, cefotaxime, and ceftriaxone, two to cefuroxime and cefotaxime, and one to ceftriaxone, cefotaxime, and ceftazidime. These cephalosporins have identical or similar side chains. Specifically, cefuroxime, ceftriaxone, and cefotaxime —like cefepime and cefodizime—have a methoxyimino group in their R1 side chains [60, 61]. Moreover, cefotaxime, ceftriaxone, cefodizime, and cefepime share identical R1 side chains (Fig. 2).

In the aforementioned studies [10, 11, 15, 17, 27], however, cephalosporin-allergic subjects did not undergo challenges with alternative cephalosporins found negative in allergy tests.

Recently, we assessed the cross-reactivity and tolerability of alternative cephalosporins in 102 subjects with an IgE-mediated hypersensitivity to cephalosporins [30••]. Our work-up included skin tests with the classic benzylpenicillin reagents, ampicillin, amoxicillin, 11 different cephalosporins (cephalexin, cefaclor, cefadroxil, cefazolin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, cefepime, and ceftibuten), and any other responsible cephalosporin, as well as serum-specific IgE assays and challenges.

Subjects were classified in four groups according to their patterns of allergy test positivity: group A, positive to one or more of ceftriaxone, cefuroxime, cefotaxime, cefepime, cefodizime, and ceftazidime; group B, positive to aminocephalosporins; group C, positive to cephalosporins other than those belonging to the aforementioned groups; and group D, positive to cephalosporins belonging to two different groups. Specifically, 73 subjects were classified as group A, 13 as group B, 7 as group C, and 9 as group D.

With regard to group A, 41 subjects were positive only to the responsible cephalosporins (mainly to ceftriaxone), whereas 32 displayed different patterns of cross-reactivity. In group B, 11 had positive responses only to the responsible compound (nine to cefaclor and two to cephalexin), whereas two presented a pattern of cross-reactivity. In these two groups, cross-reactivity appeared to be connected with similar or identical R1 side chains (Fig. 2). In group C, six subjects were positive only to the responsible compound (five to cefazolin and one to cefamandole), and the remaining subject, who had

reacted to cefoperazone, was positive to both cefoperazone and cefamandole, which share an identical R2 side chain (Fig. 2). The nine subjects of group D showed different patterns of positivity, most of which could not be explained by similar or identical side chains, suggesting the possibility of coexisting sensitivities.

In any case, group A subjects underwent challenges with cefaclor, cefazolin, and ceftibuten; group B with cefuroxime axetil, ceftriaxone, cefazolin, and ceftibuten; group C with cefaclor, cefuroxime axetil, ceftriaxone, cefazolin, and ceftibuten, except those who had reacted to cefazolin, who were not challenged with it; and group D subjects underwent challenges with some of the aforementioned cephalosporins selected on the basis of their patterns of positivity.

A total of 323 challenges with alternative cephalosporins were well tolerated by the 102 subjects. This study demonstrated that cephalosporin hypersensitivity is not a class hypersensitivity. Two groups (or subclasses) of cephalosporins were identified: group A, which included cephalosporins with a methoxyimino group in their R1 side chains plus ceftazidime, and group B, which was composed of aminocephalosporins (Fig. 2). The limited number of subjects sensitive to cephalosporins other than those belonging to the aforementioned groups did not allow us to identify further groups. On the basis of the case of the subject positive to both cefoperazone and cefamandole, however, one could hypothesize additional groups, such as one consisting of cephalosporins like cefamandole, cefoperazone, and cefotetan which share an identical R2 side chain with a *N*-methyl-tetrazole-thiol group.

This study also demonstrated that in subjects with an IgE-mediated hypersensitivity to cephalosporins, the risk of positive allergy test responses with alternative cephalosporins is not connected only with the structural similarities among their side-chain determinants.

In any case, cephalosporin-allergic subjects might be treated with alternative cephalosporins that have side chains different from those of the responsible compounds and are negative in pre-treatment skin tests.

Cross-Reactivity between Cephalosporins and Other BLs

A few studies evaluated cross-reactivity between cephalosporins and the other classes of BLs by administering the alternative BLs found negative in allergy tests to subjects with an IgE-mediated hypersensitivity to cephalosporins. In the aforesaid Spanish study [17], two of the 24 subjects allergic to cephalosporins were skin test positive to penicillin determinants, while 22 were skin test negative to them and tolerated benzylpenicillin challenges. More recently, we evaluated 98 subjects with an IgE-mediated hypersensitivity to cephalosporins, mostly ceftriaxone, ceftazidime, and cefotaxime, by performing skin tests and serum-specific IgE assays with penicillins, as well as skin tests with aztreonam, imipenem/cilastatin, and meropenem [26••]. Positive allergy test results to penicillins were displayed by 25 subjects (25.5 %), including one with positive results to all reagents tested and another with a positive result to aztreonam. An additional subject had experienced two anaphylactic reactions to both ceftazidime and aztreonam and had positive results to both these BLs, which share an identical side chain (Figs. 1 and 2). Nevertheless, none of the other ten subjects of this study [26••] who were allergic to ceftazidime had a positive skin test result for aztreonam.

Of the 25 subjects positive to penicillins, 14 were positive only in the ImmunoCAP. However, the ImmunoCAP results concerning these 14 subjects could have entailed an overestimation of the number of subjects with cephalosporin allergy who were also sensitive to penicillins, because positive results in the ImmunoCAP do not always predict a clinical reaction.

Negative subjects underwent challenges with amoxicillin, aztreonam, imipenem/cilastatin, and meropenem: only one reacted to imipenem/cilastatin, experiencing an urticarial reaction even though she was negative in skin testing.

This study demonstrated that after reacting to a cephalosporin that shares a similar or identical side chain with penicillins, the estimated relative risk ratio of cross-reacting with at least one penicillin was 3.0 (95 % CI = 1.6 to 5.5 %).

Finally, in a study that assessed 105 adults reporting nonimmediate reactions to cephalosporins [62], a T-cell-mediated hypersensitivity was diagnosed in six subjects on the basis of positive responses to patch tests and/or delayed-reading intradermal tests. Cross-reactivity between cephalexin and aminopenicillins was observed in two of the six subjects who had experienced maculopapular rashes associated with cephalexin therapy.

Conclusions

Cross-reactivity among BLs, especially between penicillins and cephalosporins, seems to be mainly related to side chain similarity or identity. However, considering that the rate of cross-reactivity even between penicillins and cephalosporins, such as amoxicillin and cefadroxil that share an identical side chain, does not reach 40 % [9], the mechanistic basis of cross-reactivity is likely to be more complex than only being related to a side chain. Modeling and crystallography studies of the 3D structure may lead to the discovery of novel antigens residing also in parts of the molecule other than the side chain. In this connection, compounds with dissimilar structures, yet similar biosostere properties (similar 3-dimensional electronic and steric properties), might result in cross-reactivity, as observed between the benzyl group of penicillin G and the thiophene side chain of cephalothin [2••, 42, 61].

On the other hand, the cross-reactivity related to the selective recognition by IgE or T lymphocytes of the BL ring appears to be exceptional. In effect, such recognition would entail positive responses to all BLs tested. This kind of response was not observed in studies concerning cross-reactivity and tolerability of cephalosporins, carbapenems, or aztreonam in subjects with a T-cell-mediated hypersensitivity to penicillins [45, 47, 49, 50••, 54, 55•, 59]. When considering subjects with an IgE-mediated hypersensitivity to BLs, in studies that evaluated a total of more than 400 adults—demonstrating an absence [28•] or a very low rate (around 1 %) [18, 20] of allergic cross-reactivity between penicillins and carbapenems, as well as between cephalosporins and carbapenems [26••]—only two subjects presented positive skin tests to both imipenem/cilastatin and meropenem and were also skin test positive to all the other BLs tested, including aztreonam. Therefore, their IgE antibodies were probably directed against a common nuclear determinant, the BL ring (Fig. 1). One of these two subjects, who had participated in the two studies concerning cross-reactivity between penicillins and imipenem/cilastatin [18] or meropenem [20], had also participated in a study of ours [14] which had assessed cross-reactivity between penicillins and cephalosporins, displaying positive responses to skin tests with all penicillin reagents and cephalosporins tested (Table 2).

Finally, we must consider that some patterns of positivity found in studies concerning cross-reactivity among BLs, which cannot be explained by either the common BL ring or by similar or identical side chains, indicate the possibility of coexisting sensitivities.

Compliance with Ethical Standards

Conflict of Interest Drs. Romano, Gaeta, Arribas Poves, and Valluzzi declare no conflicts 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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- •• Of major importance

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