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

Antonino Romano, MD,[a,b] Francesco Gaeta, MD,[a] Rocco Luigi Valluzzi, MD,[a] Michela Maggioletti, MD,[a] Cristiano Caruso, MD,[a] and Donato Quaratino, MD[c] *Rome, Troina, and Capranica, Italy*

Background: The few studies performed in adults with T cell–mediated hypersensitivity to penicillins have found a rate of cross-reactivity with cephalosporins ranging from 2.8% to 31.2% and an absence of cross-reactivity with aztreonam.
Objective: We sought to evaluate the possibility of using cephalosporins and aztreonam in subjects with documented delayed hypersensitivity to penicillins who especially require them.
Methods: We conducted a prospective study of 214 consecutive subjects who had 307 nonimmediate reactions to penicillins (almost exclusively aminopenicillins) and had positive patch test and/or delayed-reading skin test responses to at least 1 penicillin reagent. To assess cross-reactivity with cephalosporins and aztreonam and the tolerability of such alternative β-lactams, all subjects underwent skin tests with cephalexin, cefaclor, cefadroxil, cefuroxime, ceftriaxone, and aztreonam. Subjects with negative responses were challenged with the alternative β-lactams concerned.
Results: All subjects had negative skin test results to cefuroxime, ceftriaxone, and aztreonam and tolerated challenges. Forty (18.7%) of the 214 subjects had positive skin test responses to at least 1 aminocephalosporin. Of the 174 subjects with negative responses, 170 underwent challenges; 1 reacted to cefaclor.
Conclusions: These data demonstrate a rate of cross-reactivity between aminopenicillins and aminocephalosporins (ie, cephalexin, cefaclor, and cefadroxil) of around 20%, as well as the absence of cross-reactivity between penicillins and cefuroxime, ceftriaxone, and aztreonam in all subjects with T cell–mediated hypersensitivity to penicillins, almost exclusively aminopenicillins. Therefore these subjects could be treated with cefuroxime, ceftriaxone, and aztreonam. In those who especially require cephalosporin or aztreonam treatment, however, we recommend pretreatment skin tests because negative responses indicate tolerability. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Aztreonam, cephalosporins, challenges, cross-reactivity, nonimmediate reactions, penicillins, tolerability, skin tests*

Abbreviations used
MDM: Minor determinant mixture
TEN: Toxic epidermal necrolysis

Penicillins are the antibiotics that most frequently provoke hypersensitivity reactions mediated by a T-cell pathogenic mechanism, usually occurring more than 1 hour after drug administration (ie, nonimmediate).[1,2] The most frequent reactions are maculopapular or morbilliform exanthemas, particularly during treatment with amoxicillin or ampicillin. A T cell–mediated pathogenic mechanism has also been demonstrated in other nonimmediate reactions, such as acute generalized exanthematous pustulosis and toxic epidermal necrolysis (TEN).[3,4]

Studies performed since 1990 on samples of at least 30 subjects with a documented IgE-mediated hypersensitivity to penicillins have demonstrated a rate of positive responses to skin tests[5-8] or serum specific IgE assays[9] with cephalosporins ranging from 0% (0/41 subjects)[6] to 27.1% (73/269 subjects).[9] In some of these studies,[5-8] participants with penicillin allergy and negative skin test responses with cephalosporins, such as cephalexin, cefazolin, cefuroxime, ceftazidime, and ceftriaxone, underwent challenges with the cephalosporins concerned. Of a total of 241 subjects, only 2 in the study by Caimmi et al[8] reacted to cefuroxime.

In other studies[10-13] patients with penicillin allergy underwent challenges with cephalosporins, such as cefamandole, cephalexin, cefadroxil, and ceftriaxone, without performing skin tests with the cephalosporin concerned. The highest rate of positive challenges (38%) was observed in the study by Miranda et al,[12] who administered cefadroxil to 21 subjects allergic to amoxicillin.

As far as T cell–mediated hypersensitivity to penicillins is concerned, 5 studies assessed cross-reactivity with cephalosporins in a total of 240 adults with such hypersensitivity by performing delayed reading skin tests, patch tests, or both with cephalosporins and, in case of negative responses, challenges.[14-18] In these studies the rate of positive responses to cephalosporin allergologic tests ranged from 2.8% (2/71 subjects)[17] to 31.2% (5/16).[15]

Few studies have evaluated cross-reactivity with aztreonam in samples larger than 10 subjects with IgE-mediated hypersensitivity to penicillins, performing allergologic tests and challenges with it in a total of 297 such subjects.[19-22] In 2 of these studies,[19,20] 3 participants had positive allergologic test responses with aztreonam; 2 of them tolerated aztreonam challenges, whereas the third participant did not undergo the challenge. In

From [a]the Allergy Unit, Complesso Integrato Columbus, Rome; [b]IRCCS Oasi Maria S.S., Troina; and [c]Ambulatorio di Allergologia, IDI-IRCCS, Capranica.

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Corresponding author: Antonino Romano, MD, Unità di Allergologia, Complesso Integrato Columbus, Via G. Moscati, 31, 00168 Rome, Italy. E-mail: aromano.allergy@gmail.com.

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these studies,[19-22] of a total of 294 subjects with negative skin test responses to aztreonam, 293 underwent challenges and tolerated them.

Four studies did not find any cross-reactivity with aztreonam in subjects with T cell–mediated hypersensitivity to penicillins.[14,16,18,23] Specifically, the largest of these studies[18] evaluated 97 subjects with such hypersensitivity by performing both patch tests and delayed-reading skin tests with aztreonam. None of these participants had positive responses to aztreonam allergologic tests; 72 of them underwent aztreonam challenges and tolerated them.

The present prospective study was conducted to evaluate the possibility of using cephalosporins and aztreonam in patients with a documented T cell–mediated allergy to penicillins. To address this question, a large group of such subjects was evaluated by using delayed-reading skin tests with cephalosporins (cephalexin, cefaclor, cefadroxil, cefuroxime, and ceftriaxone) and aztreonam to assess the cross-reactivity. Subjects with negative responses were challenged to ascertain whether negative responses could be a reliable indicator of the tolerability of these alternative β-lactams.

METHODS

Patient selection

We studied all participants older than 14 years who were recruited to the allergy units of the Complesso Integrato Columbus, Rome, Italy; Oasi Maria Santissima, Troina, Italy; and Istituto Dermopatico dell'Immacolata, Capranica, Italy between January 2000 and June 2014 because of histories of nonimmediate reactions to penicillins. The inclusion criterion was a positive patch test and/or delayed-reading skin test response to at least 1 penicillin reagent. An indication for cephalosporin or aztreonam treatment was not a criterion of inclusion. Exclusion criteria were pregnancy and severe cardiovascular, renal, or respiratory compromise. Before the study, all subjects received information about possible risks of allergologic tests, and written informed consent was obtained from each patient or the parents of those less than 18 years of age. The respective institutional review boards approved the protocol.

Skin and patch tests

On the first day, skin prick and intradermal tests were carried out with penicilloyl-polylysine (Allergopharma, Reinbeck, Germany), minor determinant mixture (MDM; Allergopharma), and benzylpenicillin (Grünenthal Pharma AG, Mitlödi, Switzerland). The final concentrations were 5×10^{-5} mol/L, 2×10^{-2} mol/L, and 10,000 IU/mL, respectively. Because Allergopharma ceased production of penicillin reagents, from July 2005, we used Diater S.A. (Madrid, Spain) reagents: penicilloyl-polylysine (final concentration, 1.07×10^{-2} mol/L) and MDM (benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid; final concentration, 1.5 mol/L). Since May 2011, the composition of MDM has changed and now contains only sodium benzylpenicilloate.

Patch tests were also administered with benzylpenicillin, ampicillin, and amoxicillin (5% in petrolatum; F.I.R.M.A., Florence, Italy); piperacillin (at a concentration of 200 mg/mL in 0.9% NaCl) was also used in subjects with adverse reactions to it, as previously described.[24,25]

Two days later, ampicillin (Amplital, Pfizer Srl, Latina, Italy) and amoxicillin (Amoxil, GlaxoSmithKline, Brentford, United Kingdom), at concentrations of 1 and 20 mg/mL, after dilution in 0.9% NaCl, were used for skin prick and intradermal tests. Piperacillin (Piperital; Istituto Biochimico Italiano S.p.A., Aprilia, Italy) at concentrations of 1 and 20 mg/mL, after dilution in 0.9% NaCl was also used in subjects with adverse reactions to it, as previously described.[25]

In subjects with positive patch test responses to 1 or more of the aforementioned semisynthetic penicillins, only the concentration of 1 mg/mL was used.

On a different day, all subjects with positive patch and/or delayed-reading skin test responses underwent skin testing with aztreonam (Primbactam, Guidotti, Pisa, Italy), cephalexin (Keforal, Crinos S.p.A., Milan, Italy), cefaclor (Panacef, Valeas, Milan), cefadroxil (Duracef, Juste, S.A.Q.F., Madrid), cefuroxime (GlaxoSmithKline, Verona, Italy), and ceftriaxone (Fidia farmaceutici S.p.A., Abano Terme, Italy) at a concentration of 2 mg/mL in 0.9% NaCl. After June 2004, we used cephalexin, cefaclor, and cefadroxil at concentrations of 2 and 20 mg/mL in 0.9% NaCl.

For injectable compounds, we used the intravenous form under sterile conditions, whereas for noninjectable cephalosporins, we prepared a solution, as previously described.[26]

The concentrations used for cephalosporins proved to be nonirritating in previous studies.[26-32]

We also administered patch tests with cephalexin, cefaclor, and cefadroxil at 5% in petrolatum (F.I.R.M.A.).

In skin tests all reagents were initially tested on volar forearm skin by using the skin prick method, and reactions were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema was present 20 minutes later. When skin prick test responses were negative, 0.02 mL of the reagent solution was injected intradermally on volar forearm skin, and readings were made at 20 minutes and 48 hours. Positive controls for skin prick and intradermal tests were performed with histamine (10 and 1 mg/mL, respectively); normal saline was used as a negative control, as previously described.[24]

Responses on intradermal tests were considered positive when an increase of greater than 3 mm in initial wheal diameter accompanied by erythema was present 20 minutes later.[33] Late reactions to intradermal tests were considered positive when an infiltrated erythema with a diameter of greater than 5 mm was present.[4]

In patch testing all reagents were applied to uninvolved skin on the interscapular region of the patient's back by using acrylate adhesive strips with small plates attached for test allergens (Curatest, Lohmann GmbH & Co. KG, Neuwied, Germany), as previously described.[24,25] Occlusion time was 48 hours. Readings of patch tests were made 15 minutes after removal of the strips and 48 hours later. Positive reactions were scored as follows: + (erythema, infiltration, possibly discrete papules), ++ (erythema, infiltration, papules, and vesicles), and +++ (intense erythema, infiltration, and coalescing vesicles).[4,33]

Aztreonam and cephalosporin controlled administrations (challenges)

In participants with negative allergologic test responses with the alternative β-lactams concerned, we performed controlled intramuscular administrations of therapeutic doses of aztreonam (1 g) and ceftriaxone (1 g), as well as oral administrations of cefuroxime axetil (500 mg), cephalexin (1 g), cefaclor (500 mg), and cefadroxil (500 mg), each on a different day and in the above order. We administered an initial dose of one hundredth of the therapeutic dose. In cases with negative responses, 1 week later, we administered a dose of one tenth and, if the responses were again negative, after another week a full dose, as previously described.[4,31,34] After the first 30 challenges with each β-lactams, we modified this workup, administering an initial dose of one tenth of the therapeutic dose, and if the response was negative, we administered a full dose 1 week later. After 30 additional challenges, we administered an initial dose of one tenth of the therapeutic dose, and, if the response was negative, we administered a full dose 1 hour later.

In case of a positive response to an aminocephalosporin, the other doses were not administered. Challenges with aminocephalosporins were not performed in subjects who had experienced TEN or acute generalized exanthematous pustolosis.

Patients were carefully monitored during all allergy testing and for 6 hours after challenges. They were also advised to return to show any positive responses.

Statistical analysis

We collected the data prospectively and analyzed them with Stata software (StataCorp, College Station, Tex). Our goal was to assess the cross-reactivity with cephalosporins and aztreonam and its potential determinants in patients

TABLE I. Clinical data of the 214 patients

	All patients (n = 214)	Cross-reactive (n = 40)	Non–cross-reactive (n = 174)
Age (y), mean (SD); range	42.2 (17); 15-79	42.7 (13.5); 16-74	42 (17.7); 15-79
Female sex, no. (%)	146 (68.2)	34 (85)	112 (64.4)
Time since last drug reaction,* median (range [25th-75th percentile])	12 (1-540 [4-96])	18 (2-396 [6-84])	12 (1-540 [3-96])
Family history of allergic disease, no. (%)	84 (39.2)	12 (30)	72 (41.4)
Personal history of allergic disease, no. (%)	49 (22.9)	9 (22.5)	40 (23)

Responsible β-lactams, no. (%)	All reactions (n = 307)	Reactions in cross-reactive patients (n = 62)	Reactions in non–cross-reactive patients (n = 245)
Amoxicillin	172 (56 [91 plus clavulanic acid])	27 (43.5 [9 plus clavulanic acid])	145 (59.2 [82 plus clavulanic acid])
Ampicillin	91 (29.6 [7 plus sulbactam, 2 plus cloxacillin, 1 plus flucloxacillin])	26 (41.9 [1 plus sulbactam])	65 (26.5 [6 plus sulbactam, 2 plus cloxacillin, 1 plus flucloxacillin])
Bacampicillin	29 (9.4)	9 (14.5)	20 (8.2)
Piperacillin	4 (1.3)	0	4 (1.6)
Benzylpenicillin	3 (1)	0	3 (1.2)
Benzathine penicillin	1 (0.3)	0	1 (0.4)
Pivampicillin	1 (0.3)	0	1 (0.4)
Unknown	6 (1.9)	0	6 (2.4)

Manifestation, no. (%)	All reactions (n = 307)	Reactions in cross-reactive patients (n = 62)	Reactions in non–cross-reactive patients (n = 245)
Maculopapular exanthema	146 (47.5)	24 (38.7)	122 (49.8)
Maculopapular exanthema plus edema	114 (37.1)	23 (37.1)	91 (37.1)
Erythema	14 (4.5)	2 (3.2)	12 (4.9)
Erythema plus edema	7 (2.3)	4 (6.4)	3 (1.2)
Edema	6 (1.9)	2 (3.2)	4 (1.6)
TEN	5 (1.6)	2 (3.2)	3 (1.2)
AGEP	3 (1)	3 (4.8)	0
Bullous exanthema	3 (1)	1 (1.6)	2 (0.8)
Local reaction	3 (1)	0	3 (1.2)
Urticaria	2 (0.6)	1 (1.6)	1 (0.4)
Others	4 (1.3)	0	4 (1.6)

Positive patch test and/or delayed-reading skin test results, no. (%)	All patients (n = 214)	Cross-reactive patients (n = 40)	Non–cross-reactive patients (n = 174)
Penicilloyl-polylysine†	5 (2.3)	2 (5)	3 (1.7)
MDM	8 (3.7)	3 (7.5)	5 (2.9)
Benzylpenicillin	97 (45.3)	26 (65)	71 (40.8)
Ampicillin	212 (99.1)	40 (100)	172 (98.9)
Amoxicillin	210 (98.1)	40 (100)	170 (97.7)
Piperacillin	4 (1.9)	0	4 (2.3)

AGEP, Acute generalized exanthematous pustulosis.
*Time (in months) elapsed between the last adverse penicillin reaction and current allergologic examination.
†Positivity of immediate reading skin test responses.

with documented T cell–mediated hypersensitivity to penicillins. We have presented the frequency of positive responses as a percentage and exact 95% CI. We have compared the group of patients who were cross-reactive with those who were not. Age has been reported as means ± SDs, and the time interval between the last adverse reaction and testing has been reported as the median and range. We presented categorical data as the number of cases and percentages and compared them by using the χ^2 test. We have calculated the odd ratios and corresponding 95% CIs to assess the determinants significantly associated with cross-reactivity.

RESULTS

We examined a total of 214 participants, who constituted 37% of an outpatient population of 578 adults with histories of nonimmediate reactions to penicillins; 154 of the 214 subjects also participated in our other study of patients with penicillin allergy.[34] None of these cases had any exclusion criterion. The responsible penicillins and clinical manifestations are shown in Table I. Two hundred eight (97.2%) subjects reported hypersensitivity reactions to aminopenicillins (amoxicillin, ampicillin, bacampicillin, or pivampicillin), and 6 of them also reported hypersensitivity reactions to other penicillins. Of the remaining 6 participants, 3 reacted to piperacillin and 3 to benzylpenicillin. Overall, 129 subjects had only 1 reaction to penicillins, whereas 77 participants had 2 reactions, and 8 had 3 reactions.

All subjects had positive patch test and/or delayed-reading skin test responses to at least 1 penicillin reagent. The patterns of skin test and patch test reactivity in the 214 patients are summarized in Table II.

Our 214 subjects had negative skin test responses to cefuroxime, ceftriaxone, and aztreonam; 40 (18.7% [95% CI, 14% to 24.4%]) of them had positive skin test responses to at least 1 aminocephalosporin. Fifteen of these 40 subjects also displayed positive responses to patch tests with aminocephalosporins (Table III).

TABLE II. Patterns of skin test and patch test reactivity in the 214 patients with delayed hypersensitivity to penicillins

Patients (no.)	Delayed intradermal test						Patch test			
	PPL	MDM	BP	AM	AX	Culprit	BP	AM	AX	Culprit
92	−	−	−	+	+	+	−	+	+	+
39	−	−	+	+	+	+	−	+	+	+
36	−	−	+	+	+	+	+	+	+	+
11	−	−	−	+	+	+	−	−	−	−
6	−	+	+	+	+	+	+	+	+	+
3	−	−	−	+	+	+	−	+	−	−
3	−	−	+	+	+	+	−	−	−	−
3	−	−	+	NP	NP	NP	−	+	+	+
2	−	−	−	NP	NP	NP	−	+	+	+
2	−	−	NP	NP	NP	NP	+	+	+	+
2	−	−	+	+	+	+	+	−	−	−
2	+*	−	−	+	+	+	−	+	+	+
2	+*	−	+	+	+	+	−	+	+	+
1	+*	+	−	+	+	+	−	+	+	+
1	−	+	−	+	+	+	−	+	+	+
1	−	−	−	+	+	+	−	+	+	−
1	−	−	+	+	−	+	+	−	−	+
1	−	−	+	+	+	+	−	+	−	+
1	−	−	+	+	−	+	+	+	−	−
1	−	−	−	−	+	+	−	+	+	+
1	−	−	+	−	−	+	+	−	−	−
1	−	−	−	−	−	+	−	−	−	+
1	−	−	−	+	+	+	−	+	−	−
1	−	−	−	−	+	+	−	+	−	+
Positive patients (no.)	5	8	95	203	203	207	49	195	188	191

AM, Ampicillin; *AX*, amoxicillin; *BP*, benzylpenicillin; *NP*, not performed (subjects who had experienced TEN or acute generalized exanthematous pustulosis and displayed positive responses to patch tests with the penicillin concerned); *PPL*, penicilloyl-polylysine.
*Positivity of immediate reading skin test results.

None of the 214 subjects experienced systemic reactions to skin or patch tests.

The frequency of participants' characteristics did not significantly differ between patients with either positive or negative skin test responses for cephalosporins; the exception was skin test positivity to benzylpenicillin, which occurred in 26 of 40 (65% [95% CI, 49.4% to 77.9%]) patients and 71 of 174 (40.8% [95% CI, 33.8% to 48.2%]) patients with and without cross-reactivity, respectively (Table I). The estimated odds ratio of skin test positivity to benzylpenicillin for cross-reacting to at least 1 cephalosporin was 2.69 (95% CI, 1.31 to 5.51).

Of our 214 subjects with negative responses to cefuroxime, ceftriaxone, and aztreonam, 213 accepted challenges and tolerated them (100% [95% CI, 98.2% to 100%]). Of the 174 subjects with negative responses to aminocephalosporins, 170 underwent challenges with them; only 1 reacted, experiencing a maculopapular exanthema 24 hours after the full dose of cefaclor. Three participants were not challenged because they experienced TEN. One subject, who had maculopapular exanthemas associated with ampicillin and amoxicillin, refused challenges with the alternative β-lactams.

DISCUSSION

Before the present study, 5 studies[14-18] assessed cross-reactivity with cephalosporins in adults with a T cell–mediated hypersensitivity to penicillins, and 4 studies[14,16,18,23] evaluated cross-reactivity with aztreonam in such subjects. In effect, our results confirm those of the latter 4 studies[14,16,18,23] by the same group, which did not find any cross-reactivity between penicillins and aztreonam. However, our study contains the important finding of the absence of cross-reactivity between penicillins (almost exclusively aminopenicillins) and both cefuroxime and ceftriaxone. This finding differs from those of other studies, which found positive responses to patch tests[14,18] or challenges[17] with cephalosporins, such as cefixime, cefpodoxime, and cefuroxime, which have side chains different from those of penicillins. Moreover, before performing challenges, we assessed all our 214 patients by using both delayed-reading skin tests (skin prick and intradermal tests) and patch tests with cephalexin, cefaclor, and cefadroxil, as well as by using delayed-reading skin tests with cefuroxime and ceftriaxone, whereas other studies assessed cross-reactivity with cephalosporins by using only patch tests[15,17] or patch tests and delayed-reading skin prick tests.[14,16,18] This is very important as regards the negative predictive value of the allergy workup. In the present study, in effect, delayed-reading intradermal tests have proved to be more sensitive than skin prick tests and patch tests, as observed in previous studies, which assessed subjects with nonimmediate reactions to β-lactams, especially cephalosporins.[24,31,35] All this might explain the fact that we observed only 1 subject with a positive challenge response to cefaclor among the 213 participants who underwent a total of 935 challenges with cephalosporins found to elicit negative responses in the allergy workup.

With regard to cephalosporins, based on positive responses to delayed-reading intradermal tests and challenges, the present study found a 19.1% rate (41/214 subjects) of cross-reactivity between penicillins, almost exclusively aminopenicillins, and aminocephalosporins. Positivity to benzylpenicillin was a statistically significant predictor because the risk for having a positive skin test response to at least 1 aminocephalosporin was increased about 3-fold.

The time interval between the last adverse reaction and the allergologic examination did not significantly differ between patients with either positive or negative skin test responses for cephalosporins, confirming literature data indicating that, in evaluating nonimmediate reactions to β-lactams, responses of allergologic examinations do not appear to be influenced by such a time interval.[4,24] In a previous study of ours,[24] which assessed adults with either immediate or nonimmediate reactions to aminopenicillins, we demonstrated that the mean time interval between the most recent reaction and the allergologic tests was significantly longer in the delayed-type than in the IgE-mediated type responses. Moreover, some studies re-evaluated patients with a T cell–mediated hypersensitivity to penicillins from 1 year to more than 6 years after the first allergologic examination, observing that only 2 (1.8%) of 108 patients had responses that became negative.[35-38]

The aforementioned rate of cross-reactivity is very similar to that (18.5% [18/97 participants]) observed in a recent study by Buonomo et al,[18] who evaluated subjects with a T cell–mediated hypersensitivity to penicillins by performing both delayed-reading prick tests and patch tests with cephalexin and cefaclor. In this study[18] 15 (15.5%) of the 97 participants had positive patch test responses to at least 1 of the aforementioned aminocephalosporins; of the 82 subjects with negative responses, 36 underwent

TABLE III. Clinical data and allergologic test responses of the 40 subjects with positive patch test and/or skin test responses with aminocephalosporins

Patient no.	Sex	Age	Drug involved	Type of reaction	Delayed intradermal test			Patch test		
					CH	CE	CD	CH	CE	CD
1	M	36	AX	ER	+	+	−	−	+	−
2	F	53	AX; AM	MP/ED; MP/ED	i 20	i 20	i 20	−	−	−
3	F	27	AM; AX	ED; ER/ED	+	+	+	+	+	+
4	F	53	BC; AM	MP/ED; MP	+	+	+	+	+	+
5	M	16	AX+clav; AX+clav	MP; MP	−	i 20	−	−	−	−
6	F	38	AM	MP	−	i 20	−	−	−	−
7	F	20	AX+clav	MP	−	i 20	−	−	−	−
8	F	45	BC; AM	U; BU	+	+	+	+	+	−
9	F	37	AX+clav; AX	MP/ED; MP	i 20	i 20	−	+	+	−
10	F	30	AX	TEN	i 20	+	−	−	−	−
11	F	34	BC	MP/ED	+	+	−	+	+	−
12	F	43	AM; AX	MP/ED; MP	i 20	+	−	−	−	−
13	F	44	BC; AX	MP; MP	−	+	−	−	−	−
14	F	66	AM	TEN	+	+	+	+	+	+
15	M	59	BC	MP	+	+	−	−	+	−
16	F	43	AM	MP/ED	i 20	+	−	−	−	−
17	F	56	AM; AX	MP/ED; MP/ED	+	+	−	−	−	−
18	F	60	BC	MP/ED	+	+	−	−	+	−
19	F	51	AM	MP	+	+	+	−	−	−
20	F	21	AX; AM	MP/ED; MP/ED	i 20	i 20	i 20	−	−	−
21	F	42	AX	AGEP	i 20	i 20	−	−	−	−
22	F	37	AM; AM	MP; MP	−	−	i 20	−	−	−
23	M	32	AX+clav	MP	−	+	−	−	−	−
24	F	39	BC; AM	MP/ED; MP/ED	i 20	+	+	−	−	−
25	F	45	AX; AX	AGEP; AGEP	+	+	+	+	+	+
26	F	53	AX+clav	MP/ED	+	+	−	+	+	−
27	F	39	AM; AM	MP; MP	+	+	−	+	+	−
28	F	56	BC; AX	ER/ED; MP/ED	+	+	+	−	−	−
29	F	74	AX; AX+clav	MP/ED; ED	i 20	i 20	i 20	−	−	−
30	F	33	AM+sulb	MP	−	+	−	−	−	−
31	F	67	AX+clav; AX	MP; MP	−	+	+	−	−	−
32	M	40	AX+clav; AM; AM	ER; ER/ED; ER/ED	+	+	i 20	+	+	+
33	F	26	AM	MP/ED	+	+	−	+	+	−
34	F	47	AM	MP	−	i 20	−	−	−	−
35	F	28	BC	MP/ED	+	+	+	−	−	−
36	F	56	AX; AM	MP; MP/ED	+	+	+	−	−	−
37	F	51	AM	MP/ED	i 20	i 20	−	−	−	−
38	F	24	AM; AM	MP/ED; MP	+	+	−	−	+	−
39	M	45	AX	MP/ED	i 20	+	−	−	−	−
40	F	44	AM; AX	MP; MP	i 20	+	+	−	−	−
				Positive patients (no.)	31	39	17	11	15	5

AGEP, Acute generalized exanthematous pustulosis; *AM*, ampicillin; *AX*, amoxicillin; *BC*, bacampicillin; *BU*, bullous exanthema; *CD*, cefadroxil; *CE*, cefaclor; *CH*, cephalexin; *clav*, clavulanic acid; *E*, erythema; *ED*, edema; *ER/ED*, erythema plus edema; *F*, female; *i 20*, positivity only to intradermal test at 20 mg/mL; *M*, male; *MP*, maculopapular exanthema; *MP/ED*, maculopapular exanthema plus edema; *sulb*, sulbactam; *U*, urticaria.

challenges with cephalexin, and 3 reacted. The higher rate of patients with positive aminocephalosporin skin test responses found in the present study (18.7% [40/214 participants]) can be explained mainly by the fact that, unlike Buonomo et al,[18] in addition to skin prick tests and patch tests, we performed delayed-reading intradermal tests with 3 different aminocephalosporins up to a concentration of 20 mg/mL. It should be noted that this concentration allowed us to diagnose a sensitization to aminocephalosporins in 11 subjects, who might have been missed at a concentration of 2 mg/mL (Table III).

On the other hand, our data indicate the absence of cross-reactivity between penicillins and cefuroxime, ceftriaxone, and aztreonam in subjects with delayed hypersensitivity to penicillins. As previously observed, therefore, we confirmed the absence of cross-reactivity between penicillins and aztreonam found in previous studies performed in subjects with such hypersensitivity.[14,16,18,23] However, we did not confirm the data of the aforementioned study[18] that found 6 participants with positive patch test responses to cephalosporins other than aminocephalosporins, such as cefuroxime axetil and cefixime; 4 of these 6 participants had positive responses to cefaclor, cephalexin, or both.

It should also be noted that in the study by Trcka et al,[17] 2 of the 71 patients with delayed hypersensitivity to aminopenicillins and negative patch test responses to cefpodoxime and cefixime who underwent challenges with these cephalosporins had an exanthema with cefpodoxime and cefixime, respectively.

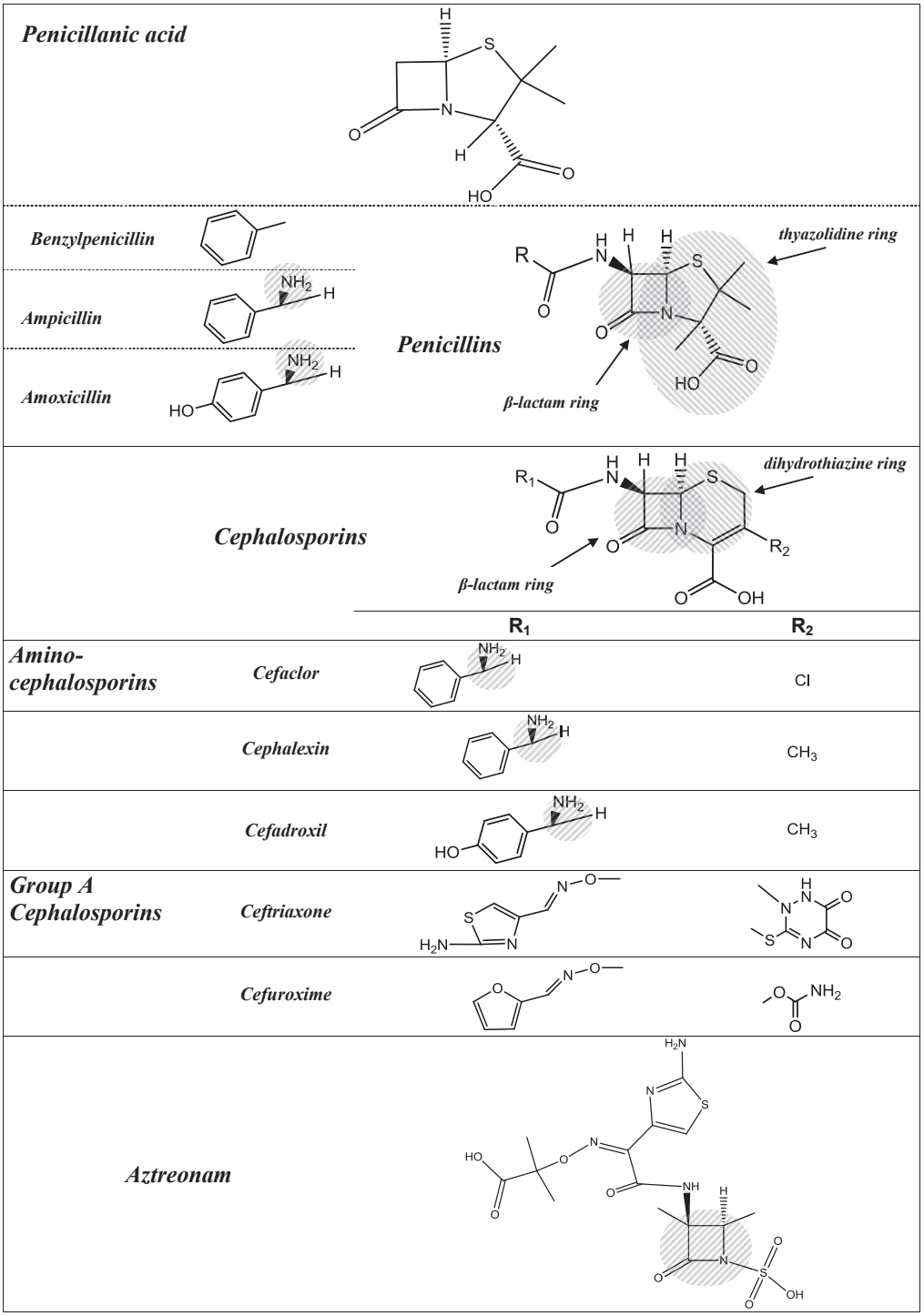

FIG 1. Chemical structures of penicillins, cephalosporins, and aztreonam, with the amino group, common β-lactam ring, dihydrothiazine ring, and thiazolidine ring highlighted in *gray*.

As far as aztreonam is concerned, early immunogenicity studies[39,40] demonstrated that it is weakly immunogenic and does not cross-react with penicillin and cephalosporin antibodies, except for ceftazidime, with which it shares an identical side chain.

With regard to cefuroxime and ceftriaxone, the absence of cross-reactivity with penicillins can be explained by the fact that the T cells of patients with penicillin allergy recognize specific penicillin determinants rather than a common nuclear determinant (ie, the β-lactam ring), which is shared by penicillins, cephalosporins, and aztreonam (Fig 1). Indeed, Padovan et al[41] investigated the reactivity of penicillin-induced human T-cell clones to various penicillin derivatives, demonstrating that the antigenic epitope of penicillins recognized by T cells consists

of both the side-chain structure and the thiazolidine ring. In this *in vitro* study[41] the complete absence of the side chain in 6-aminopenicillanic acid (Fig 1) resulted in the inability to stimulate T-cell clones from patients with penicillin allergy.

All this can explain the cross-reactivity with aminocephalosporins found in the present study. In effect, ampicillin and amoxicillin share identical or similar side chains with cephalexin, cefaclor, and cefadroxil, whereas penicillins do not share common side chains with cefuroxime, ceftriaxone, and aztreonam (Fig 1). Therefore the positive responses to patch tests or challenges with cephalosporins, such as cefixime, cefpodoxime, and cefuroxime, with side chains unlike those of penicillins, as observed in previous studies,[14,17,18] can be explained with coexisting sensitivities, as previously observed in both patients with penicillin[7] and those with cephalosporin[42] allergies. It is unlikely that these positive responses to cephalosporins, which have side-chain structures different from those of penicillins, can be related to a sensitization to the common β-lactam ring. In fact, such a pattern of sensitization (ie, selective recognition by T lymphocytes of the β-lactam ring) would entail positive responses to all β-lactams tested, which were observed neither in the present study nor in previous studies concerning cross-reactivity and tolerability of cephalosporins, carbapenems, or aztreonam in subjects with T cell–mediated hypersensitivity to penicillins.[14-18,23,34]

On the contrary, when considering subjects with IgE-mediated hypersensitivity to β-lactams in studies that demonstrated a very low (around 1%) rate of allergic cross-reactivity between penicillins and carbapenems,[43,44] as well as between cephalosporins and carbapenems,[42] the 2 subjects with positive skin test responses to both imipenem/cilastatin and meropenem also had positive responses to all the other β-lactams tested, including aztreonam; therefore their IgE antibodies were probably directed against a common nuclear determinant, the β-lactam ring (Fig 1).

Considering that aminopenicillins were the responsible penicillins in 97.2% of subjects assessed and that the present study found a rate of cross-reactivity with aminocephalosporins of around 20%, the mechanistic basis of cross-reactivity is likely to be more complex than only being related to an amino side chain. Modeling and crystallography studies of the 3-dimensional structure might lead to uncovering of novel antigens residing also in parts of the molecule other than the amino side chain.

An important limitation of our study is that challenges were not followed by full therapeutic courses because we studied our patients for research purposes rather than for clinical indications for alternative β-lactam treatment.

In any case, delayed-reading intradermal testing with alternative β-lactams, such as cephalosporins and aztreonam, is a simple and reliable tool for identifying cross-reactive subjects. Considering the results of the present study, patch testing with cephalosporins, because of its low sensitivity, is not advisable for assessing any cross-reactivity in subjects with a T cell–mediated hypersensitivity to penicillins.

In conclusion, our study demonstrated a rate of cross-reactivity between penicillins and aminocephalosporins of around 20%, as well as the absence of cross-reactivity between penicillins and cefuroxime, ceftriaxone, and aztreonam in all subjects with a T cell–mediated hypersensitivity to penicillins, almost exclusively aminopenicillins. Therefore these subjects could be treated with cefuroxime, ceftriaxone, and aztreonam. Nevertheless, until further studies confirm our data, in patients with such hypersensitivity who need these alternative β-lactams, we recommend pretreatment skin tests. Considering that only 1 of our challenged patients had a cutaneous reaction and only at the full dose of cefaclor, graded challenges are not required when aztreonam and cephalosporins (eg, especially cefuroxime and ceftriaxone), which have side chains different from those of penicillins, are administered to patients with penicillin allergy who have negative pretreatment skin test responses to these alternative β-lactams.

Clinical implications: Subjects with T cell–mediated hypersensitivity to penicillins could be treated with aztreonam and cephalosporins, which have side-chain determinants different from those of the responsible compounds and elicit negative responses on pretreatment skin tests.

REFERENCES

1. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. J Allergy Clin Immunol 2011; 127(suppl):S67-73.
2. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International consensus on drug allergy. Allergy 2014;69:420-37.
3. Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med 2003;139: 683-93.
4. Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, et al. Diagnosis of non-immediate reactions to β-lactam antibiotics. Allergy 2004;39: 1153-60.
5. Audicana M, Bernaola G, Urrutia I, Echechipia S, Gastaminza G, Muñoz D, et al. Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. Allergy 1994; 49:108-13.
6. Novalbos A, Sastre J, Cuesta J, De Las Heras M, Lluch-Bernal M, Bombín C, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. Clin Exp Allergy 2001;31:438-43.
7. Romano A, Guéant-Rodriguez RM, Viola M, Pettinato R, Guéant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. Ann Intern Med 2004;141:16-22.
8. Caimmi S, Galéra C, Bousquet-Rouanet L, Arnoux B, Demoly P, Bousquet PJ. Safety of cefuroxime as an alternative in patients with a proven hypersensitivity to penicillins: a DAHD cohort survey. Int Arch Allergy Immunol 2010;153:53-60.
9. Liu XD, Gao N, Qiao HL. Cephalosporin and penicillin cross-reactivity in patients allergic to penicillins. Int J Clin Pharmacol Ther 2011;49:206-16.
10. Blanca M, Fernandez J, Miranda A, Terrados S, Torres MJ, Vega JM, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunologic studies. J Allergy Clin Immunol 1989;83:381-5.
11. Sastre J, Quijano LD, Novalbos A, Hernandez G, Cuesta J, de las Heras M, et al. Clinical cross-reactivity between amoxicillin and cephadroxil in patients allergic to amoxicillin and with good tolerance of penicillin. Allergy 1996;51:383-6.
12. Miranda A, Blanca M, Vega JM, Moreno F, Carmona MJ, García JJ, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. J Allergy Clin Immunol 1996;98:671-7.
13. Park MA, Koch CA, Klemawesch P, Joshi A, Li JT. Increased adverse drug reactions to cephalosporins in penicillin allergy patients with positive penicillin skin test. Int Arch Allergy Immunol 2010;153:268-73.
14. Patriarca G, D'Ambrosio C, Schiavino D, Larocca LM, Nucera E, Milani A. Clinical usefulness of patch and challenge tests in the diagnosis of cell-mediated allergy to betalactams. Ann Allergy Asthma Immunol 1999;83:257-66.
15. Phillips E, Knowles SR, Weber EA, Blackburn D. Cephalexin tolerated despite delayed aminopenicillin reactions. Allergy 2001;56:790.
16. Schiavino D, Nucera E, De Pasquale T, Roncallo C, Pollastrini E, Lombardo C, et al. Delayed allergy to aminopenicillins: clinical and immunological findings. Int J Immunopathol Pharmacol 2006;19:831-40.
17. Trcka J, Seitz CS, Bröcker EB, Gross GE, Trautmann A. Aminopenicillin-induced exanthema allows treatment with certain cephalosporins or phenoxymethyl penicillin. J Antimicrob Chemother 2007;60:107-11.
18. Buonomo A, Nucera E, Pecora V, Rizzi A, Aruanno A, Pascolini L, et al. Cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins. J Investig Allergol Clin Immunol 2014;24:331-7.

19. Moss RB. Sensitization to aztreonam and cross-reactivity with other beta-lactam antibiotics in high-risk patients with cystic fibrosis. J Allergy Clin Immunol 1991;87:78-88.
20. Vega JM, Blanca M, García JJ, Miranda A, Carmona MJ, García A, et al. Tolerance of aztreonam in patients allergic to betalactam antibiotics. Allergy 1991;46: 196-202.
21. Patriarca G, Schiavino D, Lombardo C, Altomonte G, De Cinti M, Buonomo A, et al. Tolerability of aztreonam in patients with IgE-mediated hypersensitivity to beta-lactams. Int J Immunopathol Pharmacol 2008;21:375-9.
22. Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Caruso C, Romano A. Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to penicillins. J Allergy Clin Immunol 2015;135:972-6.
23. Buonomo A, Nucera E, De Pasquale T, Pecora V, Lombardo C, Sabato V, et al. Tolerability of aztreonam in patients with cell-mediated allergy to β-lactams. Int Arch Allergy Immunol 2011;155:155-9.
24. Romano A, Quaratino D, Di Fonso M, Papa G, Venuti A, Gasbarrini G. A diagnostic protocol for evaluating nonimmediate reactions to aminopenicillins. J Allergy Clin Immunol 1999;103:1186-90.
25. Romano A, Gaeta F, Valluzzi RL, Caruso C, Rumi G, Bousquet PJ. The very limited usefulness of skin testing with penicilloyl-polylysine and the minor determinant mixture in evaluating nonimmediate reactions to penicillins. Allergy 2010;65:1104-7.
26. Romano A, Guéant-Rodriguez RM, Viola M, Amoghly F, Gaeta F, Nicolas JP, et al. Diagnosing immediate reactions to cephalosporins. Clin Exp Allergy 2005;35: 1234-42.
27. Romano A, Quaratino D, Venemalm L, Torres MJ, Venuti A, Blanca M. A case of IgE-mediated hypersensitivity to ceftriaxone. J Allergy Clin Immunol 1999;104: 1113-4.
28. Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol 2003; 112:629-30.
29. Antunez C, Blanca-López N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montañez MI, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. J Allergy Clin Immunol 2006;117:404-10.
30. Testi S, Severino M, Iorno ML, Capretti S, Ermini G, Macchia D, et al. Nonirritating concentration for skin testing with cephalosporins. J Investig Allergol Clin Immunol 2010;20:171-2.
31. Romano A, Gaeta F, Valluzzi RL, Caruso C, Alonzi C, Viola M, et al. Diagnosing nonimmediate reactions to cephalosporins. J Allergy Clin Immunol 2012;129: 1166-9.
32. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. J Allergy Clin Immunol 2015;136: 865-91.e3.
33. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002;57:45-51.
34. Romano A, Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Zaffiro A, et al. Absence of cross-reactivity to carbapenems in patients with delayed hypersensitivity to penicillins. Allergy 2013;68:1618-21.
35. Torres MJ, Sánchez-Sabaté E, Álvarez J, Mayorga C, Fernández J, Padial A, et al. Skin test evaluation in nonimmediate allergic reactions to penicillins. Allergy 2004;59:219-24.
36. Romano A, Di Fonso M, Pietrantonio F, Pocobelli D, Giannarini L, Del Bono A, et al. Repeated patch testing in delayed hypersensitivity to beta-lactam antibiotics. Contact Dermatitis 1993;28:190.
37. Patriarca G, Schiavino D, Nucera E, Milani A. Positive allergological tests may turn negative with no further exposure to the specific allergen: a long-term, prospective, follow-up study in patients allergic to penicillin. J Invest Allergol Clin Immunol 1996;6:162-5.
38. Romano A, Viola M, Bousquet JP, Gaeta F, Valluzzi R, Caruso C, et al. A comparison of the performance of two penicillin reagent kits in the diagnosis of β-lactam hypersensitivity. Allergy 2007;62:53-8.
39. Adkinson NF Jr, Swabb EA, Sugerman AA. Immunology of the monobactam aztreonam. Antimicrob Agents Chemother 1984;25:93-7.
40. Saxon A, Swabb EA, Adkinson NF Jr. Investigation into the immunologic cross-reactivity of aztreonam with other beta-lactam antibiotics. Am J Med 1985;78:19-26.
41. Padovan E, Mauri-Hellweg D, Pichler WJ, Weltzien HU. T cell recognition of penicillin G: structural features determining antigenic specificity. Eur J Immunol 1996;26:42-8.
42. Romano A, Gaeta F, Valluzzi RL, Caruso C, Rumi G, Bousquet PJ. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. J Allergy Clin Immunol 2010;126: 994-9.
43. Romano A, Viola M, Guéant-Rodriguez RM, Gaeta F, Pettinato R, Guéant JL. Imipenem in patients with immediate hypersensitivity to penicillins. N Engl J Med 2006;354:2835-7.
44. Romano A, Viola M, Guéant-Rodriguez RM, Gaeta F, Valluzzi R, Guéant JL. Brief communication: tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillins. Ann Intern Med 2007;146:266-9.