

Cross-Reactivity and Tolerability of Cephalosporins in Patients with IgE-Mediated Hypersensitivity to Penicillins



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What is already known about this topic? Penicillin-allergic subjects may cross-react with cephalosporins, especially with those that share identical or similar side chains with the responsible penicillins.

What does this article add to our knowledge? Thirty-nine percent of patients with penicillin allergy had positive allergy tests to cephalosporins, almost all of which were to drugs with similar or identical side chains as the responsible penicillins. Challenges with cefuroxime and ceftriaxone were well tolerated in 244 patients with negative skin tests to those drugs.

How does this study impact current management guidelines? Subjects with an IgE-mediated hypersensitivity to penicillins can be treated with cephalosporins with dissimilar side chains found negative in pretreatment skin testing.

BACKGROUND: Studies performed since 1990 on samples of at least 30 subjects with a documented IgE-mediated hypersensitivity to penicillins have found a rate of positive responses to allergy tests with cephalosporins ranging from 0% to 27%.

OBJECTIVE: We sought to assess the cross-reactivity with cephalosporins and evaluate the possibility of using cephalosporins in penicillin-allergic subjects.

METHODS: We conducted a prospective study of 252 consecutive subjects who had suffered 319 immediate reactions (mostly anaphylaxis) to penicillins and had positive skin tests to at least 1 penicillin reagent. All patients underwent serum specific IgE assays for cefaclor, as well as skin tests with 3 aminocephalosporins (cephalexin, cefaclor, and cefadroxil), cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, and cefepime. Patients with negative results for the last 5 cephalosporins were challenged with cefuroxime axetil and ceftriaxone; those with negative results for aminocephalosporins were also challenged with cefaclor and cefadroxil.

RESULTS: Ninety-nine participants (39.3%) had positive allergy tests for cephalosporins. Specifically, 95 (37.7%) were positive to aminocephalosporins and/or cefamandole, which share similar or identical side chains with penicillins. All 244 subjects who underwent challenges with cefuroxime axetil and ceftriaxone tolerated them. Of the 170 patients who underwent aminocephalosporin challenges, 3 reacted to cefaclor and 4 to cefadroxil.

CONCLUSIONS: Cross-reactivity between penicillins and cephalosporins seems to be mainly related to side chain similarity or identity. Subjects with an IgE-mediated hypersensitivity to penicillins could be treated with cephalosporins such as cefuroxime and ceftriaxone that have side-chain determinants different from those of penicillins and are negative in pretreatment skin testing. © 2018 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1662-72)

Key words: Cephalosporins; Challenges; Cross-reactivity; Immediate reactions; Penicillins; Skin tests; Tolerability

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Funding was obtained from MURST, (Italian) Ministry for University, Scientific and Technological Research.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 9, 2017; revised January 10, 2018; accepted for publication January 12, 2018.

Available online February 3, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.01.020>

Penicillins are the β -lactam antibiotics that most frequently provoke hypersensitivity reactions with an IgE-mediated pathogenic mechanism, usually occurring within 1 hour after drug administration (ie, immediate).^{1,2}

The basic structure of all β -lactams consists of a 4-membered β -lactam ring. In penicillins, it is attached to a 5-membered thiazolidine ring; the side chain (R) distinguishes the different penicillins (Figure 1). Instead of the 5-membered thiazolidine ring of penicillins, cephalosporins have a 6-membered sulfur-containing dihydrothiazine ring and 2 side chains (R1 and R2), which distinguish the different compounds (Figure 1).

The literature data regarding the extent of cross-reactivity between penicillins and cephalosporins vary greatly and are often inaccurate.³ Therefore, some confusion still exists about

Abbreviations used

BP-OL- Benzylpenicilloyl-octa-L-lysine

CI- Confidence interval

MD- Minor determinant

MDM- Minor determinant mixture

PPL- Benzylpenicilloyl-poly-L-lysine

administering cephalosporins in penicillin-allergic patients, which may lead to either under- or overestimating the risk involved.⁴

A meta-analysis of studies performed between 1966 and 2005, which compared hypersensitivity reactions with 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.⁵ However, the contamination of these early (introduced before 1980) cephalosporins with trace amounts of benzylpenicillin may have entailed an overestimation of the degree of cross-reactivity between these β -lactams. Moreover, this meta-analysis⁵ also included retrospective studies, in which the diagnosis of penicillin allergy was based only on the clinical history. In any case, this study⁵ indicated that the incidence of cross-reactivity with cephalosporins in penicillin-allergic patients varied with the similarity of the cephalosporin's side chain to that of benzylpenicillin or the responsible semisynthetic penicillin.

Studies performed since 1990 on samples of at least 30 subjects with a documented IgE-mediated hypersensitivity to penicillins⁶⁻⁹ have demonstrated a rate of positive responses to skin tests with cephalosporins ranging from 0%^{7,9} to 14.7%⁶ (Table 1). Specifically, the highest rate of positive responses to skin tests was observed in the study by Audicana et al,⁶ in which 5 of 34 penicillin-allergic patients were positive to cephalaxin.

In these studies,⁶⁻⁹ penicillin-allergic participants displaying negative results to skin tests with cephalosporins underwent challenges with the cephalosporins concerned. Of a total of 453 challenges, only 2 (0.4%) were positive (Table 1). In other studies,¹⁰⁻¹³ patients with a documented penicillin allergy underwent challenges or treatments with cephalosporins, such as cephalexin, cefadroxil, cefamandole, and ceftriaxone, without undergoing skin tests with the cephalosporin concerned. The highest rate of cephalosporin reactions (38%) was observed in the study by Miranda et al,¹² who administered cefadroxil to 21 subjects allergic to amoxicillin.

According to a recent review on cross-reactivity in β -lactam allergy,¹⁴ cross-reactivity between penicillins and cephalosporins occurs rarely, and when it occurs, it is due to similarity in the R1 side chain of the molecules.

The present prospective study was conducted to evaluate the cross-reactivity between penicillins and cephalosporins, as well as the possibility of using the latter, in patients with a documented IgE-mediated allergy to penicillins. To address this question, a large group of such subjects was evaluated by serum specific IgE assays for cefaclor, as well as skin tests with 3 amino-cephalosporins (ie, cephalexin, cefaclor, and cefadroxil), cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, and cefepime, to assess the cross-reactivity. Patients with negative

results for the last 5 cephalosporins were challenged with cefuroxime axetil and ceftriaxone; those with negative results for aminocephalosporins were also challenged with cefaclor and cefadroxil to ascertain if negative results could be a reliable indicator of the tolerability of these alternative β -lactams.

METHODS

Patients

We studied all participants older than 13 years of age who came to the allergy units of the Presidio Columbus, Rome, Italy; Oasi Maria Santissima, Troina, Italy; and Istituto Dermatologico dell'Immacolata, Capranica, Italy, between January 2009 and December 2014 because of histories of immediate reactions to penicillins. The inclusion criterion was a positive skin test result to at least 1 penicillin reagent. An indication for cephalosporin treatment was not a criterion of inclusion. The exclusion criteria were as follows: a history of hypersensitivity reactions to cephalosporins, pregnancy, use of β -blockers, and severe cardiovascular, renal, or respiratory compromise. Before the study, all subjects received information about possible risks of allergy tests, and a written informed consent was obtained from each patient or the parents of those below 18 years of age. The respective institutional review boards approved the protocol.

Skin tests

We performed skin testing on 3 different days, as previously described.¹⁵

On the first day, prick and intradermal tests were carried out using benzylpenicilloyl-poly-L-lysine (PPL, DAP, Diater, Leganés, Spain), minor determinant mixture (MDM: benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid), and benzylpenicillin. The final concentrations were 1.07×10^{-2} mol/L (ie, undiluted), 1.5 mol/L (ie, undiluted), and 10,000 IU/mL, respectively. Since May 2011 the composition of DAP has changed and includes the major determinant benzylpenicilloyl-octa-L-lysine (BP-OL) at 0.04 mg/mL (8.64×10^{-5} mol/L) and the minor determinant (MD) sodium benzylpenicilloate at 0.5 mg/mL (1.5×10^{-3} mol/L).

On the second day, we tested ampicillin and amoxicillin, at concentrations of 1 and 20 mg/mL after dilution in 0.9% NaCl. Piperacillin, 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.¹⁶

On the third day, subjects with positive skin tests to penicillin reagents were tested with a panel of 9 cephalosporins: cephalexin, cefaclor, and cefadroxil, at concentrations of 2 and 20 mg/mL; cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, and cefepime, at a concentration of 2 mg/mL. We diluted all reagents with 0.9% NaCl no more than 2 hours before administration, as previously described.¹⁵ All of the above reagents were initially tested by the prick method. A small drop of each reagent was applied on volar forearm skin, and a standardized 1-mm-tipped lancet (pricker) was passed through the drop and perpendicularly inserted into the skin. The lancet was then withdrawn and the drop gently wiped off with a paper tissue immediately thereafter. A separate pricker was used for each prick test to avoid carryover of reagents. Reactions were considered positive when a wheal larger than 3 mm in diameter with a surrounding erythema and a negative response to the control saline was present 20 minutes later. When prick tests were negative, intradermal tests were performed according to the following procedure. A volume of 0.02 mL of each reagent solution concerned

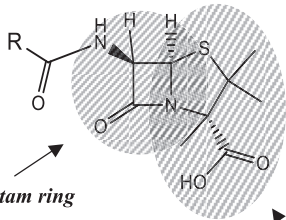
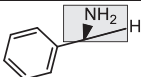
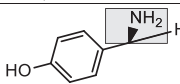
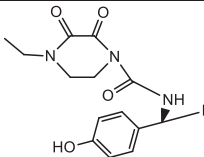
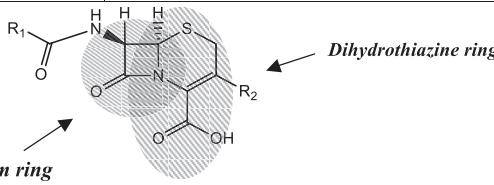
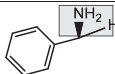
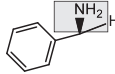
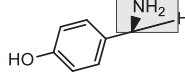
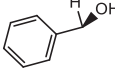
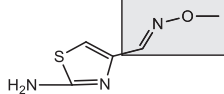
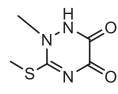
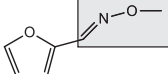
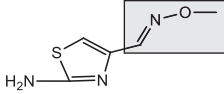
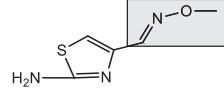
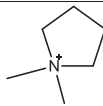
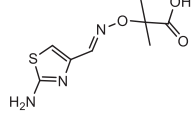
<i>Benzylpenicillin</i>		 <i>β-Lactam ring</i> <i>Thiazolidine ring</i> <i>Penicillin</i>	
<i>Ampicillin</i>			
<i>Amoxicillin</i>			
<i>Piperacillin</i>			
<i>Cephalosporins</i>	 <i>β-Lactam ring</i> <i>Dihydrothiazine ring</i> <i>R₁</i> <i>R₂</i>		
<i>Aminocephalosporins</i>	<i>Cefaclor</i>		Cl
	<i>Cephalexin</i>		CH ₃
	<i>Cefadroxil</i>		CH ₃
<i>Other cephalosporins</i>	<i>Cefamandole</i>		
	<i>Ceftriaxone</i>		
	<i>Cefuroxime</i>		
	<i>Cefotaxime</i>		
	<i>Cefepime</i>		
	<i>Ceftazidime</i>		

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

was injected intradermally on the volar forearm to produce a small superficial bleb approximately 2 mm in diameter. A tuberculin syringe with a 4/10 gauge needle penetrating the superficial layers of the skin at an angle of approximately 10° to 15° was used for intradermal administrations. Readings were made 20 minutes after injections. The wheal of the injected area was outlined on a

transparent adhesive tape immediately and 20 minutes after testing. Results were considered positive when the longest diameter of the wheal produced by the injection increased by 3 mm or more, accompanied by erythema.¹⁷ The longest wheal diameter was calculated by measuring the straight line connecting the 2 most distant points of the wheal.

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

Study (reference)	Patients, n	Skin testing		Positive patients,* n (%)	Challenge		
		Penicillin reagents	Cephalosporin(s)		Administered cephalosporin(s)	Administration route	Reactions, n/challenges, n (%)
Audicana et al ⁶	34	PPL, MDM, ampicillin, amoxicillin	Cephalexin, ceftazidime	5 (14.7)	Cephalexin, ceftazidime	Oral, intravenous	0/29 0/30
Novalbos et al ⁷	41	PPL, MDM, benzylpenicillin, amoxicillin	Cefazolin, cefuroxime, ceftriaxone	0	Cefazolin, cefuroxime, ceftriaxone	Intramuscular, intramuscular, intramuscular	0/41 0/41 0/41
Romano et al ⁸	128	PPL, MDM, benzylpenicillin, ampicillin, amoxicillin, piperacillin	Cephalothin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime	14 (10.9)	Cefuroxime axetil, ceftriaxone	Oral, intramuscular	0/101 0/101
Caimmi et al ⁹	69	PPL, MDM, benzylpenicillin, amoxicillin	Cefuroxime	0	Cefuroxime axetil	Oral	2/69 (2.9)
Present study	252	PPL/BP-OL, MDM/MD, benzylpenicillin, ampicillin, amoxicillin, piperacillin	Cephalexin, cefadroxil, cefaclor, cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, cefepime	84 (33.3)	Cefuroxime axetil, ceftriaxone, cefaclor, cefadroxil	Oral, intramuscular, oral, oral	0/244 0/244 3/170 (1.8) 4/167 (2.4)
Total	524			103 (19.6)			9/1,278 (0.7)

BP-OL, Benzylpenicilloyl-octa-L-lysine; MD, minor determinant; MDM, minor determinant mixture; PPL, benzylpenicilloyl-poly-L-lysine.

*Patients with positive skin tests to at least 1 cephalosporin.

The concentrations used for cephalosporins had proved to be nonirritating in previous studies.^{15,18-25}

Positive controls for prick and intradermal tests were done with histamine (at 10 and 1 mg/mL, respectively). As a negative control for prick and intradermal tests, normal saline was used.

Detection of total and specific IgE in serum

We performed assays for serum total and specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor with ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) in all subjects. We considered a positive result to be a value of 0.35 kU/L or greater.

Cephalosporin controlled administrations (challenges)

Challenges with cefuroxime axetil (orally) and ceftriaxone (intramuscularly) were carried out in subjects who displayed negative results for cefuroxime, ceftazidime, ceftriaxone, cefotaxime, and cefepime. Challenges with cefaclor and cefadroxil (orally) were also performed in subjects who displayed negative results on skin testing with cephalexin, cefaclor, and cefadroxil, as well as on the cefaclor ImmunoCAP.

Challenges were performed each on a different day and in the above order. In case of a positive response to cefaclor, cefadroxil was not administered.

As far as cefuroxime axetil and ceftriaxone are concerned, we administered an initial dose of one-tenth of the maximum single unit dose (500 mg and 1 g, respectively), and thus 50 mg of cefuroxime axetil or 0.1 g of ceftriaxone, each on a different day. In cases with negative results, 1 hour later we administered a full dose. We started administering one-tenth of the maximum single unit dose because in a previous study of ours⁸ all 101 penicillin-allergic patients who displayed negative results in skin tests for cefuroxime, ceftazidime, ceftriaxone, and cefotaxime and accepted graded challenges with cefuroxime axetil and ceftriaxone at an initial dose of one-hundredth of the maximum single unit dose tolerated them.

With regard to cefaclor and cefadroxil, we administered an initial dose of one-hundredth of the maximum single unit dose (500 mg), and therefore 5 mg of cefaclor and cefadroxil, each on a different day. In cases with negative results, 1 hour later we administered one-tenth (50 mg) of the maximum single unit dose, and if the result was again negative 1 hour later, we gave a full 500 mg dose. After the first 50 challenges, we modified the challenge protocol and gave initially one-tenth (50 mg) of the maximum single unit dose, and if the result was again negative 1 hour later, we gave a full 500 mg dose.

Patients were carefully monitored during all allergy testing, and for 3 hours after challenges, complete equipment for cardiopulmonary resuscitation was immediately available.

Patients with positive results for cefuroxime, ceftriaxone, cefotaxime, ceftazidime, or cefepime were not challenged with cefuroxime axetil and ceftriaxone because such positivity indicates sensitization and previous studies^{19,21,24} had found a cross-reactivity related to structural similarities in the aforesaid cephalosporins (Figure 1). In addition, participants positive to even one of the tested aminocephalosporins were not challenged with cefaclor and cefadroxil because such positivity indicates sensitization; moreover, aminocephalosporins share an amino group in their R1 side chains (Figure 1) and cross-reactions among them had been observed.²⁴

Statistical analysis

We collected the data prospectively and analyzed them using Stata software (StataCorp, College Station, Tex). Our goal was to assess the cross-reactivity with cephalosporins and its potential determinants in patients with documented IgE-mediated hypersensitivity to penicillins. We have presented the frequency of positive results as a percentage and exact 95% confidence interval (CI). We have compared the group of patients who were cross-reactive with those who were not. Age has been reported as the mean ($\pm$ standard deviation), and the time interval between the last adverse reaction and testing as the median and range. We have presented categorical

TABLE II. Characteristics of study group according to results of cephalosporin allergy tests

Clinical characteristics	All patients (n = 252)	Positivity to cephalosporin allergy tests	
		No	Yes
		Patients (n = 153)	Patients (n = 99)
Mean age $\pm$ SD, y	47.7 $\pm$ 15.7	48 $\pm$ 16.4	47.2 $\pm$ 14.7
Women, n (%)	169 (67.1)	103 (67.3)	66 (66.7)
Median time interval (range), mo* (25th, 75th percentile)	2 (1-648) (1, 7)	2 (1-648) (1, 6)	3 (1-600) (1, 8)
Family history of allergic disease, n (%)	116 (46)	72 (47.1)	44 (44.4)
Personal history of allergic disease, n (%)	58 (23)	38 (24.8)	20 (20.2)
Responsible penicillins, n (%)	All reactions (n = 319)	Reactions (n = 184)	Reactions (n = 135)
Amoxicillin	275 (86.2) (216 plus clavulanic acid)	154 (83.7) (123 plus clavulanic acid)	121 (89.6) (93 plus clavulanic acid)
Ampicillin	22 (6.9) (1 plus sulbactam)	14 (7.6)	8 (5.9) (1 plus sulbactam)
Piperacillin	8 (2.5)	7 (3.8)	1 (0.7)
Bacampicillin	5 (1.6)	4 (2.2)	1 (0.7)
Benzylpenicillin	5 (1.6)	3 (1.6)	2 (1.5)
Unknown	4 (1.3)	2 (1.1)	2 (1.5)
Manifestations, n (%)	All reactions (n = 319)	Reactions (n = 184)	Reactions (n = 135)
Anaphylaxis	229 (71.8)	129 (70.1)	100 (74.1)
Urticaria	43 (13.5)	21 (11.4)	22 (16.3)
Urticaria and angioedema	37 (11.6)	28 (15.2)	9 (6.7)
Erythema	9 (2.8)	5 (2.7)	4 (3)
Edema	1 (0.3)	1 (0.5)	-
Positive skin test results, n (%)	All patients (n = 252)	Patients (n = 153)	Patients (n = 99)
PPL/BP-OL	32 (12.7)	18 (11.8)	14 (14.1)
MDM/MD	35 (13.9)	18 (11.8)	17 (17.2)
Benzylpenicillin	86 (34.1)	51 (33.3)	35 (35.4)
Amoxicillin	228 (90.5)	137 (89.5)	91 (91.9)
Ampicillin†	176 (69.8)	96 (62.7)	80 (80.8)
Cefadroxil	62 (24.6)	—	62 (62.6)
Cefaclor	38 (15.1)	—	38 (38.4)
Cephalexin	33 (13.1)	—	33 (33.3)
Cefamandole	11 (4.4)	—	11 (11.1)
Ceftriaxone	6 (2.4)	—	6 (6.1)
Cefotaxime	3 (1.2)	—	3 (3)
Cefuroxime	2 (0.8)	—	2 (2)
Ceftazidime	—	—	—
Cefepime	—	—	—
Positive specific IgE assay results, n (%)	All patients (n = 252)	Patients (n = 153)	Patients (n = 99)
Positive patients,‡ n (%)	98 (38.9)	57 (37.3)	41 (41.4)
Penicilloyl G	79 (31.3)	42 (27.5)	37 (37.4)
Penicilloyl V	86 (34.1)	49 (32)	37 (37.4)
Ampicilloyl	114 (45.2)	67 (43.8)	47 (47.5)
Amoxicilloyl	117 (46.4)	71 (46.4)	46 (46.5)
Cefaclor	13 (5.2)	—	13 (13.1)

BP-OL, Benzylpenicilloyl-octa-L-lysine; MD, minor determinant; MDM, minor determinant mixture; PPL, benzylpenicilloyl-poly-L-lysine; SD, standard deviation.

*Time (mo) elapsed between last adverse penicillin reaction and current allergy examination.

†P = .0015 between patients who were positive to cephalosporin allergy tests and those who were negative.

‡Subjects positive to at least 1 penicillin reagent.

TABLE III. Clinical data and allergy test results of the 16 penicillin-allergic subjects with positive results to cephalosporins other than aminocephalosporins (5 of them were positive also to the latter)

Patient, n	Sex	Age	Drug involved	Type of reaction	ImmunoCAP					Skin tests													
					PG	PV	AMy	AXy	CE	PPL/BP-OL	MDM/MD	BP	AM	AX	CH	CE	CD	CM	CZ	CT	CU	CX	CP
2	F	53	AX+clav	UA	—	—	—	—	—	—	—	—	+	+	+	+	+	+	—	—	—	—	—
5	F	46	AM	U	0.39	0.43	0.37	—	—	—	—	—	+	—	—	—	—	+	—	—	—	—	—
20	M	55	AX+clav	U	—	—	—	—	—	—	—	—	+	+	+	+	+	+	—	—	—	—	—
			AX+clav	U																			
30	M	54	AX	An	—	—	22.2	6.61	0.71	—	—	+	+	+	+	+	+	+	—	+	—	—	—
45	F	14	AX	U	0.15	—	0.31	0.12	—	—	+	—	—	—	—	—	+	+	—	—	—	—	—
62	F	41	AM	UA	—	—	0.15	—	—	+	—	—	—	—	—	—	—	+	—	—	—	+	—
72	F	67	AX+clav	U	10.5	9.22	0.21	—	—	+	+	+	+	—	—	—	+	—	—	—	—	—	—
			AX+clav	U																			
73	M	28	AX	E	—	—	—	—	—	—	+	—	—	—	—	—	—	—	—	+	+	—	—
81	M	50	AX+clav	An	—	0.13	0.12	—	—	—	—	—	+	+	—	—	—	—	—	+	—	+	—
84	F	22	AX+clav	An	2.99	3.5	2.64	3.59	—	—	—	—	—	+	—	—	—	+	—	—	—	—	—
105	F	49	AM	An	—	—	—	—	—	—	—	—	+	—	—	—	—	+	—	—	—	—	—
143	F	65	AM	UA	0.17	0.26	0.23	—	—	—	—	—	+	—	—	—	—	—	—	+	+	—	—
163	F	44	AX+clav AX	An An	0.22	0.65	1.09	2.37	—	—	—	+	+	+	—	—	—	+	—	—	—	—	—
166	M	39	AX+clav	An	0.98	1.04	0.79	0.93	—	+	—	—	—	—	—	—	—	—	—	+	—	+	—
238	F	55	BP BP	UA UA	—	—	—	—	—	+	—	—	—	—	—	—	—	+	—	—	—	—	—
242	F	60	AX+clav	An	—	—	—	—	—	—	—	—	—	+	+	+	+	—	—	+	—	—	—

AM, Ampicillin; AMy, ampicilloyl; An, anaphylaxis; AX, amoxicillin; AX+clav, amoxicillin plus clavulanic acid; AXy, amoxilloyl; BP, benzylpenicillin; BP-OL, benzylpenicilloyl-octa-L-lysine; CD, cefadroxil; CE, cefaclor; CH, cephalixin; CM, cefamandole; CP, cefepime; CT, ceftriaxone; CU, cefuroxime; CX, cefotaxime; CZ, ceftazidime; E, erythema; F, female; M, male; MD, minor determinant; MDM, minor determinant mixture; PG, penicilloyl G; PPL, benzylpenicilloyl-L-lysine; PV, penicilloyl V; U, urticaria; UA, urticaria and angioedema.

TABLE IV. Clinical data and allergy test results of the 7 penicillin-allergic subjects with negative results to cephalosporins who reacted to aminocephalosporin challenges

Patient, n	Sex	Age	Drug involved	Type of reaction	ImmunoCAP					Penicillin skin tests					Positive challenges		
					PG	PV	AMy	AXy	CE	PPL/BP-OL	MDM/MD	BP	AM	AX	Culprit cephalosporin	Eliciting dose (mg)	Clinical manifestation
114	M	52	AX+clav AX+clav	U U	0.4	0.41	0.18	0.27	–	+	–	+	+	+	CE	500	U
122	F	46	AX+clav	An	0.46	0.54	0.25	0.37	–	–	–	–	+	+	CD	500	E
124	M	24	AX+clav AX+clav	U An	–	–	–	0.16	–	–	–	–	+	+	CD	50	U
167	F	49	AX+clav	An	–	–	0.12	8.3	–	–	–	–	+	+	CD	500	U
189	F	35	AX+clav AX	An An	0.11	–	–	–	–	–	–	–	–	+	CE	50	An
192	F	65	AX	UA	–	0.11	0.11	–	–	–	–	+	+	+	CE	500	E
236	F	63	AX+clav	E	–	–	–	–	–	–	–	–	–	+	CD	500	U

AM, Ampicillin; AMy, ampicilloyl; An, anaphylaxis; AX, amoxicillin; AX+clav, amoxicillin plus clavulanic acid; AXy, amoxilloyl; BP, benzylpenicillin; BP-OL, benzylpenicilloyl-octa-L-lysine; CD, cefadroxil; CE, cefaclor; E, erythema; F, female; M, male; MD, minor determinant; MDM, minor determinant mixture; PG, penicilloyl G; PPL, benzylpenicilloyl-poly-L-lysine; PV, penicilloyl V; U, urticaria; UA, urticaria and angioedema.

data as number of cases and percentages, and compared them by using a χ^2 test. A *P* value of .05 or less indicates statistical significance. We have calculated the odd ratios and the corresponding 95% CI to assess the determinants significantly associated with cross-reactivity.

RESULTS

We examined a total of 256 participants ranging in age from 14 to 80 years, with histories of immediate reactions to penicillins. These 256 subjects constituted 75.3% of an outpatient population of 340 adults recruited prospectively between January 2009 and December 2014 in the aforesaid allergy units because of such histories; 140 of the 256 subjects also participated in our other study of penicillin-allergic patients.¹⁶ Four subjects were excluded because of histories of immediate reactions to both penicillins and cephalosporins. None of the remaining 252 cases had any exclusion criterion.

The responsible penicillins and clinical manifestations are shown in Table II.

Two hundred and thirty-eight subjects (94.4%) reported hypersensitivity reactions only to aminopenicillins (amoxicillin, ampicillin, or bacampicillin), 10 to other penicillins, and the remaining 4 to both aminopenicillins and other penicillins.

The 252 participants had experienced a total of 319 immediate reactions to penicillins (Table II).

One hundred and ninety-three patients (76.6%) had had an anaphylactic reaction, which was diagnosed according to the clinical criteria proposed by Sampson et al.²⁶ The remaining 59 patients had developed only cutaneous symptoms, mostly urticaria and angioedema.

All subjects had positive skin test results to at least 1 of the penicillin reagents tested (Table II): 140 subjects were positive to only semisynthetic penicillins (ampicillin, amoxicillin, and/or piperacillin), 100 to both classic penicillin reagents (PPL/BP-OL, MDM/MD, and benzylpenicillin) and semisynthetic penicillins, and 12 only to classic penicillin reagents.

Eighty-four subjects (33.3%; CI, 27.8% to 39.4%) displayed positive skin tests to at least 1 cephalosporin. Specifically, 68 were positive only to aminocephalosporins, 11 only to cephalosporins other than aminocephalosporins, and 5 to both aminocephalosporins and other cephalosporins. With regard to the 73 participants with positive skin tests to aminocephalosporins, 27 were positive only to cefadroxil; 22 to cephalixin, cefadroxil, and cefaclor; 8 to both cefaclor and cefadroxil; 5 to both cephalixin and cefadroxil; 5 only to cefaclor; 3 to both cephalixin and cefaclor; and 3 only to cephalixin. Table III summarizes the results of allergy tests in the 16 subjects who displayed positive responses to skin tests for cephalosporins other than aminocephalosporins, mostly to cefamandole and ceftriaxone.

As far as *in vitro* assays are concerned, 98 patients (38.9%) were positive (Table II): 12 only to penicillin G and/or penicillin V, 36 only to amoxicillin and/or ampicillin, and 2 only to cefaclor. Eight subjects displayed negative skin tests for aminocephalosporins and were positive to ImmunoCAP for cefaclor.

Overall, 7 subjects presented positive skin tests for one or more of cefuroxime, ceftriaxone, and cefotaxime (Table III, subjects 30, 62, 73, 81, 143, 166, and 242), whereas 81 were positive to skin tests and/or ImmunoCAP for aminocephalosporins. Of the 245 subjects negative to cefuroxime, ceftazidime, ceftriaxone, cefotaxime, and cefepime, 244 accepted

challenges with cefuroxime axetil and ceftriaxone and tolerated them (100%; CI, 98.7% to 100%). Of the 171 participants negative to aminocephalosporins, 170 accepted challenges with cefaclor and 3 reacted. As previously said, these 3 subjects were not challenged with cefadroxil. Four of the 167 participants who underwent challenges with cefadroxil reacted to it (Table I). The clinical characteristics of the 7 subjects with positive challenges are summarized in Table IV. One participant, who had suffered an anaphylactic reaction to amoxicillin, refused cephalosporin challenges.

Overall, 99 (39.3%) of the 252 participants presented positive allergy tests for cephalosporins: 84 were positive to skin tests (5 of them also to ImmunoCAP for cefaclor), 8 were positive only to ImmunoCAP for cefaclor, and 7 reacted to challenges. Of these 99 subjects, 95 were positive to aminocephalosporins and/or cefamandole, whereas 4 only to other cephalosporins (Table III, subjects 73, 81, 143, and 166). Among the 95 subjects, 83 were positive only to aminocephalosporins (68 to skin tests, 8 only to ImmunoCAP for cefaclor, and 7 to challenges), 6 only to cefamandole (Table III, subjects 5, 72, 84, 105, 163, and 238), 3 to both aminocephalosporins and cefamandole (Table III, subjects 2, 20, and 45), 1 to aminocephalosporins, cefamandole, and ceftriaxone (Table III, subject 30), 1 to both cefamandole and cefotaxime (Table III, subject 62), and 1 to both aminocephalosporins and ceftriaxone (Table III, subject 242).

The frequency of participants' characteristics (sex, age, time interval between the last adverse reaction and allergy examination, clinical manifestations of penicillin allergy) did not significantly differ between patients with either positive or negative results on allergy tests for cephalosporins; the exception was skin test positivity to ampicillin, which occurred in 80 of 99 (80.8%; CI, 71.9% to 87.3%) and 96 of 153 (62.7%; CI, 54.8% to 70%) patients with positive and negative results, respectively (*P* = .0015). The estimated odds ratio of skin test positivity to ampicillin for cross-reacting to at least 1 cephalosporin was 2.5 (CI, 1.4-4.5).

DISCUSSION

The present study found a 39.3% rate (99/252 participants) of positive responses to allergy tests for cephalosporins in subjects with a well-demonstrated IgE-mediated hypersensitivity to penicillins (ie, with histories of immediate reactions to penicillins and a positive skin test result to at least 1 penicillin reagent). Positivity to ampicillin was a statistically significant predictor because the risk for having a positive allergy test to at least 1 cephalosporin was increased 2.5-fold. Of these 99 participants, 95 were positive to aminocephalosporins and/or cefamandole, which share similar or identical side chains with penicillins, whereas 4 were positive only to cephalosporins, such as cefuroxime, ceftriaxone, and cefotaxime, which have side chains different from those of penicillins (Figure 1).

The literature data indicate that cross-reactivity as a result of antibody recognition seems to be more closely related to side-chain identity or similarity than to the central β -lactam ring,^{14,27} although shared epitopes from other parts of the molecule also account for cross-reactivity.^{28,29} In effect, cefamandole, benzylpenicillin, and ampicillin have similar side-chain structures, which are benzyl derivatives.^{30,31} In addition, ampicillin, cephalixin, and cefaclor share an identical side chain

with an amino group, as do amoxicillin and cefadroxil (Figure 1).

In the present study, the rate of positive responses to allergy tests for cephalosporins ranges from 0% for cefepime, which has side chains different from those of the culprit penicillins and is rarely used in Italy,³² to 26.2% (66/252 participants) for cefadroxil, which shares an identical R1 side chain with amoxicillin (Figure 1), which was responsible for 86.2% of the reactions experienced by our participants.

The rate of positive responses to allergy tests for cephalosporins found in the present study (39.3%) is higher than those of the aforesaid studies,⁶⁻⁹ which evaluated cross-reactivity between penicillins and cephalosporins in subjects with an IgE-mediated hypersensitivity to penicillins. In particular, their rate is more than 3 times higher than that (10.9%) found in a previous study of ours,⁸ which assessed 128 penicillin-allergic adults (Table 1). This can be explained mainly by the fact that, unlike in the previous study,⁸ in the present study, we tested 3 aminocephalosporins that share similar or identical side-chain determinants with the aminopenicillins that were responsible for hypersensitivity reactions in the great majority (96%) of the patients assessed. We also performed assays for serum specific IgE to cefaclor with ImmunoCAP and found 8 subjects who displayed negative skin tests for aminocephalosporins and were positive to cefaclor ImmunoCAP. However, *in vitro* cross-reactivity does not predict a clinical reaction. Many patients with detectable IgE antibodies do not present these reactions.³ Indeed, false-positive test results with penicillin ImmunoCAP have been reported.^{33,34} In addition, the present study concerned a selected population of adults with immediate reactions to penicillins, more than 70% of which were anaphylactic, and with positive skin tests to penicillin reagents. Therefore, the characteristics of our study are such that its results are not comparable to those of studies regarding either individuals with an unconfirmed penicillin allergy or individuals with a demonstrated penicillin allergy among whom anaphylactic reactions are not so prevalent. In effect, in a study by Macy and Contreras,³⁵ 65,915 subjects with an unconfirmed penicillin allergy underwent 127,125 cephalosporin courses without any previous cephalosporin tolerance testing, and in 1,439 (1.1%) of the courses, a cephalosporin allergy was recorded within 30 days of their beginning. In a retrospective review of patients who received a preoperative treatment of cefazolin or cefoxitin,³⁶ only 1 (0.6%) of the 153 subjects with histories of penicillin allergy experienced an urticarial reaction to cefazolin. In another study,³⁷ there were 54 penicillin skin test positive individuals exposed to 169 therapeutic courses with unspecified cephalosporins without any cephalosporin allergy testing, and there was only 1 reaction to cefazolin. Recently, Macy and Blumenthal⁴ described 13 amoxicillin oral challenge positive individuals who tolerated 54 courses of cephalexin or cefaclor, which share a very similar R1 side chain with amoxicillin.

In any case, considering that the rate of cross-reactivity even between penicillins and cephalosporins, such as amoxicillin and cefadroxil, which share an identical side chain, does not reach 40%,¹² 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 the aforesaid study of ours⁸ and in the present study, 4 (3.1%) of 128 and 7 (2.8%) of 252 penicillin-allergic subjects, respectively, displayed different patterns of positivity to cephalosporins such as cefuroxime, ceftazidime, ceftriaxone, and cefotaxime, which have side chains different from those of penicillins. Our results demonstrate, therefore, that the risk for positive allergy tests for cephalosporins is not only related to the structural similarities between the side-chain determinants of penicillins and cephalosporins.

The positive responses to skin tests or challenges with cephalosporins that have dissimilar side chains from penicillins observed in the present study and in previous studies^{8,9} might be explained by coexisting sensitivities, as previously observed both in penicillin-⁸ and cephalosporin-allergic subjects.³⁸ It is unlikely that these positive responses to cephalosporins that have side-chain structures different from those of penicillins can be related to a sensitization toward the common β -lactam ring (Figure 1). In fact, such a pattern of sensitization (ie, selective recognition by IgE of the β -lactam ring) would entail positive responses to all β -lactams tested. When considering subjects with an IgE-mediated hypersensitivity to β -lactams, studies that evaluated a total of more than 400 adults demonstrated an absence¹⁶ or a very low (approximately 1%)^{39,40} rate of allergic cross-reactivity between penicillins and carbapenems, as well as between cephalosporins and carbapenems.³⁸ Only 2 subjects presented positive skin tests to both imipenem/cilastatin and meropenem and were also skin test positive to all the other β -lactams tested, including aztreonam. Therefore, their IgE antibodies were possibly directed against the β -lactam ring.

Considering the possibility of coexisting sensitivities, it could be risky to treat penicillin-allergic patients even with cephalosporins selected on the basis of side-chain differences. For this reason, pretreatment skin tests with the cephalosporins concerned are advisable before their administration to penicillin-allergic patients.⁸

Our data, as well as those of previous studies,⁶⁻⁹ provide a substantial clinical support to one of the 3 options of the Joint Task Force on Practice Parameters⁴¹ concerning cephalosporin administration to patients with histories of penicillin allergy. This option suggests performing skin tests with the cephalosporin concerned and, in case of negative results, giving it via a graded challenge.

However, the present study has some limitations. Even though skin tests with cephalosporins have been used in numerous studies, they are not as well validated as those with penicillins; in particular, the negative and positive predictive values of cephalosporin skin testing are not fully established.⁴¹⁻⁴³ In the present study, a total of 7 participants reacted to challenges with cefaclor or cefadroxil even though they presented negative skin tests. In addition, several previous studies^{15,21,44-46} identified patients with histories of hypersensitivity reactions to cephalosporins who reacted to challenges even though they were skin test negative to the administered cephalosporins. This might be due to the fact that in the aforesaid studies,^{15,21,44-46} as well as in the present study, only the native drugs were used for cephalosporin skin testing. Probably, in our study, skin testing with the relevant cephalosporin MDs could have helped identify those patients who reacted to challenges with cefaclor and cefadroxil. In effect, Venemalm⁴⁷ found that aminocephalosporins, such as cefaclor and cephalexin, undergo aminolysis with formation of a pyrazinone degradation product and

demonstrated that a pyrazinone-polylysine conjugate is recognized by the serum IgE of some cefaclor-allergic subjects. However, it should be noted that most MDs of cephalosporins have not been fully characterized²⁹ and thus are not available. Nevertheless, some studies^{6-9,24} demonstrated that the negative predictive value of cephalosporin skin tests when only using the native drug is very high. Specifically, in a study of ours that assessed the cross-reactivity and tolerability of alternative cephalosporins in 102 adults with an IgE-mediated hypersensitivity to cephalosporins,²⁴ a total of 323 challenges with alternative cephalosporins found negative in skin testing were well tolerated by all participants. In any case, the results of the present study suggest that the use of only the parent drugs for cephalosporin skin tests entails only a limited probability of underreporting the risk of cephalosporin hypersensitivity reactions in penicillin-allergic patients treated with the related cephalosporins found negative in skin testing.

It should also be noted that a study by Yoon et al⁴⁸ found a rate of 5% of false positivities to cephalosporin skin tests in participants with no suspicion of cephalosporin hypersensitivity. In our experience, however, cephalosporin skin tests proved to be reliable and effective for diagnosing immediate hypersensitivity to these β -lactams^{15,38} and selecting alternative cephalosporins in cephalosporin-allergic subjects.²⁴ For this reason, we do not perform challenges with cephalosporins in patients with positive results; physicians who did so elicited immediate urticarial or anaphylactic reactions to the responsible cephalosporins.^{46,49-51} Nevertheless, the lack of testing to determine the positive predictive value of skin testing with cephalosporins constitutes a limitation of the present study. Another 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 conclusion, our study demonstrated a rate of cross-reactivity among penicillins, cefamandole, and amino-cephalosporins around 38%, as well as the tolerability of cefuroxime and ceftriaxone in all subjects with IgE-mediated hypersensitivity to penicillins displaying negative skin tests with these cephalosporins. Nevertheless, until further studies confirm our data, in patients with such hypersensitivity who need these alternative β -lactams, we recommend pretreatment skin tests, because positive responses to them have been observed.

Taking into account the data of the present study, as well as those of previous ones⁶⁻⁹ (Table I), graded challenges may not be necessary when cephalosporins with dissimilar side chains are administered to penicillin-allergic patients who display negative pretreatment skin tests with these alternative β -lactams.

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