IgE-mediated hypersensitivity to cephalosporins: Cross-reactivity and tolerability of alternative cephalosporins

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Background: Studies regarding the cross-reactivity and tolerability of alternative cephalosporins in large samples of subjects with an IgE-mediated hypersensitivity to cephalosporins are lacking.
Objective: We sought to evaluate the possibility of using alternative cephalosporins in subjects with cephalosporin allergy who especially require them.
Methods: One hundred two subjects with immediate reactions to cephalosporins and positive skin test results to the responsible drugs underwent serum specific IgE assays with cefaclor and skin tests with different cephalosporins. Subjects were classified in 4 groups: group A, positive responses to 1 or more of ceftriaxone, cefuroxime, cefotaxime, cefepime, cefodizime, and ceftazidime; group B, positive responses to aminocephalosporins; group C, positive responses to cephalosporins other than those belonging to the aforementioned groups; and group D, positive responses to cephalosporins belonging to 2 different groups. Group A subjects underwent challenges with cefaclor, cefazolin, and ceftibuten; group B participants underwent challenges with cefuroxime axetil, ceftriaxone, cefazolin, and ceftibuten; and group C and D subjects underwent challenges with some of the aforementioned cephalosporins selected on the basis of their patterns of positivity.
Results: There were 73 subjects in group A, 13 in group B, 7 in group C, and 9 in group D. Challenges with alternative cephalosporins (ceftibuten in 101, cefazolin in 96, cefaclor in 82, and cefuroxime axetil and ceftriaxone in 22 subjects) were well tolerated.
Conclusions: Cephalosporin hypersensitivity does not seem to be a class hypersensitivity. Subjects with cephalosporin allergy who especially require alternative cephalosporins might be treated with compounds that have side-chain determinants different from those of the responsible cephalosporins and have negative pretreatment skin test responses. (J Allergy Clin Immunol 2015;136:685-91.)

Key words: *Cephalosporin allergy, cross-reactivity, skin tests, tolerability*

Like penicillins, cephalosporins can cause IgE-mediated reactions, which usually occur within 1 hour after the last drug administration (ie, immediate reactions)[1,2] and are generally characterized by urticaria, angioedema, rhinitis, bronchospasm, and anaphylactic shock.[3-6]

Even though skin tests with cephalosporins are not as well validated as those with penicillins,[5,7,8] several studies have demonstrated their usefulness in the diagnosis of immediate reactions to the responsible compounds.[9-16] Specifically, in 3 European studies involving only adults,[11] both children and adults,[12] and only children[13] with histories of immediate reactions to cephalosporins, the rate of positive skin test responses with the responsible cephalosporins was 69.7% (53/76 subjects), 30.7% (39/127), and 72.1% (31/43), respectively. In some studies[11,12,16,17] subjects with immediate reactions to cephalosporins were evaluated by using serum specific IgE assays and skin tests with penicillin reagents, as well as with different cephalosporins, including those responsible. Three patterns of reactivity were observed: cross-reactivity with penicillins, selective reactivity to responsible cephalosporins, and cross-reactivity with cephalosporins other than those responsible. These studies demonstrated that cross-reactivity among cephalosporins is mainly connected with R1 side chains.[11,12,16,17] Specifically, there were numerous subjects who displayed cross-reactivity among ceftriaxone, cefuroxime, cefotaxime, and ceftazidime. All these cephalosporins share similar or identical R1 side chains (see Fig E1 in this article's Online Repository at www.jacionline.org).

With regard to the tolerability of alternative cephalosporins in subjects with IgE-mediated hypersensitivity to these β-lactams, there are multiple reports of single cases or small series of subjects with histories of immediate reactions to a specific cephalosporin that were confirmed by positive skin test responses to the culprit drug and in which subjects were successfully challenged with other β-lactams, including first-, second-, and third-generation cephalosporins, to which skin test responses were negative.[15,18-31] However, studies regarding the cross-reactivity and tolerability of alternative cephalosporins in large samples of subjects with an IgE-mediated hypersensitivity to these β-lactams are lacking.

The present study was performed to evaluate the possibility of using alternative cephalosporins in subjects with cephalosporin allergy who especially require them.

METHODS

Subject selection

Subjects were recruited prospectively from an outpatient population with histories of immediate reactions to cephalosporins. To be included in the study,

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subjects had to have positive skin test responses to the responsible cephalosporins. An indication for treatment with cephalosporins other than those responsible was not a criterion of inclusion.

Exclusion criteria were pregnancy, use of β-blockers, and severe cardiovascular, renal, or respiratory compromise. Before the study, all subjects received information about the possible risks of skin tests, and written informed consent was obtained from each subject or the parents of those less than 18 years of age. The respective institutional review boards approved the protocol.

Skin prick and intradermal skin tests

We performed skin testing on 3 different days, as previously described.[11] On the first day, we carried out skin prick and intradermal tests with penicilloyl-polylysine (Diater, Madrid, Spain), minor determinant mixture (Diater), and benzylpenicillin. On the second day, we used ampicillin and amoxicillin at concentrations of 1 and 20 mg/mL after dilution in 0.9% NaCl. On the third day, we used the responsible cephalosporins (Table I). Subjects with positive skin test responses to these cephalosporins were tested with a panel of 11 cephalosporins, which could include the culprits cephalexin, cefaclor, cefadroxil, cefazolin, and ceftibuten at concentrations of 2 and 20 mg/mL or cefamandole, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, and cefepime at a concentration of 2 mg/mL. Cefoperazone and cefodizime were tested 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.[11]

Skin tests and readings were performed, as previously described.[11,32] The concentration used for cephalosporins had proved to be nonirritating in previous studies.[11-13,22,33-35]

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 (Phadia, Uppsala, Sweden, now Thermo Fisher Scientific) in all subjects. We considered a positive result to be a value of 0.35 kU/L or greater.

Cephalosporin challenges (test dosing)

Subjects were classified into 4 groups on the basis of their patterns of positivity to cephalosporins: group A, positive response to 1 or more of ceftriaxone, cefuroxime, cefotaxime, cefepime, cefodizime, and ceftazidime (ie, group A cephalosporins); group B, positive response to aminocephalosporins (ie, cefaclor and cephalexin); group C, positive response to cephalosporins other than those belonging to the aforementioned groups; and group D, positive response to cephalosporins belonging to 2 different groups.

Group A subjects underwent challenges with cefaclor, cefazolin, and ceftibuten; group B participants underwent challenges with cefuroxime axetil, ceftriaxone, cefazolin, and ceftibuten; group C subjects underwent challenges 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.

We performed controlled administrations of therapeutic doses of ceftriaxone (1 g administered intramuscularly), cefuroxime axetil (500 mg administered orally), cefazolin (1 g administered intramuscularly), cefaclor (500 mg administered orally), and ceftibuten (400 mg administered orally), each on a different day. We administered an initial dose of one-hundredth of the therapeutic dose. In cases with negative results, we administered a dose of one-tenth 1 hour later, and if the response was again negative we administered a full dose after another hour.

After the first 20 tests with each cephalosporin, we modified this workup, administering an initial dose of one-tenth of the therapeutic dose; if the result was negative, we administered a full dose 1 hour later. We carefully monitored each subject during challenges until 3 hours after the administration of the full dose, and complete equipment for cardiopulmonary resuscitation was immediately available.

TABLE I. Clinical data of the 102 subjects with cephalosporin allergy

Characteristic	All subjects (n = 102)
Age (y), mean ± SD	49.7 ± 19.4
Women, no. (%)	80 (78.4)
Time since last cephalosporin reaction,* median (range [25th, 75th percentile])	2.5 (1-360 [1, 9])
Family history of allergic disease, no. (%)	37 (36.3)
Personal history of allergic disease, no. (%)	30 (29.4)
Responsible β-lactams, no. (%)	All reactions: 112
Ceftriaxone	67 (59.8)
Cefaclor	13 (11.6)
Ceftazidime	10 (8.9)
Cefazolin	6 (5.4)
Cefotaxime	4 (3.6)
Cephalexin	3 (2.7)
Cefuroxime	3 (2.7 [2 axetil])
Cefodizime	2 (1.8)
Cefamandole	1 (0.9)
Cefoperazone	1 (0.9)
Amoxicillin	2 (1.8 [1 plus clavulanic acid])
Manifestation, no. (%)	All reactions: 112
Anaphylaxis	93 (83)
Urticaria	10 (8.9)
Erythema	4 (3.6)
Urticaria and angioedema	3 (2.7)
Bronchospasm	2 (1.8)

*Time (in months) elapsed between the last adverse cephalosporin reaction and the current allergologic examination.

Statistical analysis

We collected data prospectively and analyzed them with Stata software (StataCorp, College Station, Tex). Our goal was to assess cross-reactivity with cephalosporins other than those responsible and its potential determinants in subjects with documented cephalosporin allergy. We have presented the frequency of positive results as a percentage and exact 95% CI. We have compared the group of subjects who were cross-reactive with those who were not. Age has been reported as the mean (±SD) and the time interval between the last adverse reaction and testing as the median and range. We compared these continuous variables using the Mann-Whitney *U* test. We presented categorical data as the number of cases and percentages and compared them by using the χ^2 and Fisher exact tests. A *P* value of .05 or less indicates statistical significance. We calculated the relative risk ratios and the corresponding 95% CIs to assess the determinants significantly associated with cross-reactivity.

RESULTS

We examined 102 subjects who ranged in age from 14 to 81 years and had positive skin test responses to at least the responsible cephalosporins. These participants constituted 72.8% of an outpatient population of 140 subjects recruited prospectively between January 2005 and June 2014 in the Allergy Units of C.I. Columbus, Oasi Maria S.S., and Istituto Dermopatico dell'Immacolata because of histories of immediate reactions to cephalosporins. Twenty-seven of them were reported in a previous study of ours.[14] None of these cases had any exclusion criteria. All our subjects had been treated with penicillins some time before their cephalosporin hypersensitivity reactions.

Clinical data are summarized in Table I. The most frequent responsible compounds were ceftriaxone, cefaclor, and ceftazidime. Our 102 subjects had a total of 110 immediate reactions

TABLE II. Clinical data and allergologic test results of the 20 subjects with cephalosporin allergy and positive results to penicillin reagents

Subject no.	Sex	Age (y)	Drug involved	Type of reaction	CAP-FEIA					Skin tests						Patterns of cephalosporin reactivity*
					PG	PV	AMy	AXy	CE	PPL	MDM	BP	AM	AX	Culprit	
1	F	50	Cephalexin	An	0.43	−	−	−	−	+	+	+	+	+	+	Cross-reactive
3	F	35	Ceftazidime	An	0.63	0.56	−	−	−	−	−	−	−	−	+	Selective
7	F	61	Ceftriaxone	An	−	−	−	−	−	+	+	+	−	−	+	Selective
8	F	15	Cephalexin	U	−	−	−	−	−	+	+	+	−	−	+	Selective
9	F	47	Ceftriaxone Ceftriaxone	An U	8.02	9.27	2.57	−	−	−	−	−	−	−	+	Cross-reactive
14	F	22	Cefaclor	An	−	−	−	−	0.6	−	−	−	+	+	+	Selective
16	F	25	Cefaclor	UA	4.49	14.9	0.39	−	2.53	−	−	−	−	−	+	Selective
23	F	51	Ceftriaxone	An	1.25	2.3	0.8	0.9	−	−	−	−	−	−	+	Cross-reactive
25	F	14	Cefaclor	An	−	−	−	−	−	−	−	+	+	+	+	Cross-reactive
27	F	59	Ceftriaxone	An	−	−	−	−	−	−	−	+	−	−	+	Cross-reactive
28	F	44	Ceftriaxone	An	1.24	−	−	−	−	−	−	−	−	−	+	Cross-reactive
31	F	54	Ceftriaxone	An	−	−	1.04	−	−	−	−	−	−	−	+	Cross-reactive
33	F	69	Ceftriaxone	An	0.35	0.49	0.87	0.36	−	−	−	−	−	−	+	Cross-reactive
41	F	60	Ceftriaxone	An	−	0.55	−	−	−	+	−	−	−	−	+	Selective
45	F	72	Cephalexin AX	An E	−	−	−	−	−	−	−	−	+	+	+	Selective
57	F	50	Ceftriaxone AX + clav	An UA	−	6.45	0.4	−	11.7	−	−	+	−	+	+	Cross-reactive
62	F	33	Ceftazidime	BS	0.47	−	−	−	−	−	−	−	−	−	+	Selective
65	M	14	Cefaclor	U	−	0.63	0.35	−	0.5	−	−	−	−	−	+	Selective
81	F	77	Ceftriaxone	An	−	11.7	1.07	0.79	1.47	−	−	−	−	−	+	Cross-reactive
96	F	68	Ceftriaxone	An	−	0.36	−	0.45	−	−	−	−	−	−	+	Cross-reactive

AM, Ampicillin; *AMy*, ampicilloyl; *An*, anaphylaxis; *AX*, amoxicillin; *AXy*, amoxicilloyl; *BP*, benzylpenicillin; *BS*, bronchospasm; *CE*, cefaclor; *clav*, clavulanic acid; *E*, erythema; *F*, female; *M*, male; *MDM*, minor determinant mixture; *PG*, penicilloyl G; *PPL*, penicilloyl-polylysine; *PV*, penicilloyl V; *U*, urticaria; *UA*, urticaria and angioedema.
*Regardless of their positivity to penicillin reagents, *selective* refers to subjects with positive results only to the responsible cephalosporins, whereas *cross-reactive* refers to subjects with positive results to different cephalosporins, including those responsible. The patterns of cephalosporin cross-reactivity of the latter subjects are shown in Tables III and IV.

to cephalosporins, 1 to amoxicillin plus clavulanic acid, and 1 to amoxicillin. Ninety-two subjects had only 1 reaction to a cephalosporin, 5 had had 2 reactions to the same cephalosporin, 3 had 2 distinct reactions to different cephalosporins, and in 2 cases reactions to both cephalosporins and penicillins in separate episodes had occurred.

Eighty-nine subjects had an anaphylactic reaction, which was diagnosed according to the clinical criteria proposed by Sampson et al.[36] Of the remaining 13 subjects, 11 had cutaneous symptoms, mostly urticaria and angioedema, and 2 had experienced a bronchospasm. Data were collected at the time of the allergy visit. However, clinical records of 70 (68.6%) of the 102 participants were available: 50 from the emergency department and 20 based on hospitalization.

The clinical manifestations were mucocutaneous in 75 (84.3%) of the 89 subjects with anaphylactic reactions, respiratory in 63 (70.8%), cardiovascular in 61 (68.5%), and gastrointestinal in 20 (22.5%); simultaneous involvement of 2, 3, and 4 organ systems was observed in 53.9%, 35.9%, and 6.7% of these subjects, respectively. Specifically, hypotension occurred in 59 subjects, and loss of consciousness occurred in 35 subjects.

No delayed reactions or biphasic anaphylaxis were reported. Tryptase levels were not determined.

All 102 subjects had positive skin test responses to the responsible cephalosporins (see Table E1 in this article's Online Repository at www.jacionline.org); 9 (8.8%) of them also had positive responses to penicillin reagents (Table II).

As far as *in vitro* assays are concerned, 18 (17.6%) subjects had positive responses: 10 only to penicillin reagents, 4 only to cefaclor (the responsible cephalosporin), and 4 (2 of whom had reacted to cefaclor) to both the penicillin reagents and cefaclor.

When considering the results of both skin tests and specific IgE assays with the penicillin reagents, 20 (19.6% [95% CI, 13.1% to 28.4%]) subjects had positive responses to these reagents (Table II). We observed positive results on allergologic tests for penicillin determinants in 7 (43.7% [95% CI, 23% to 67.1%]) of the 16 subjects who reacted to cephalosporins that share similar (cefamandole) or identical (cefaclor and cephalexin) side chains with penicillins versus 13 (15.1% [95% CI, 9.1% to 24.2%]) of the 86 subjects who reacted to cephalosporins (ceftriaxone, ceftazidime, cefotaxime, cefuroxime, cefazolin, cefodizime, or cefoperazone) that have side chains different from those of penicillins ($P < .05$, Fisher exact test). 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 1 penicillin was 2.89 (95% CI, 1.37-6.11).

On the basis of the results of both cephalosporin skin tests and cefaclor-specific IgE assays, 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 had positive responses only to the responsible cephalosporins (32 to ceftriaxone, 7 to ceftazidime, and 1 to cefotaxime and cefodizime, respectively), whereas 32 displayed different patterns of cross-reactivity (Table III). Among group B subjects, 11 had positive responses only to the responsible compound (9 to cefaclor and 2 to cephalexin), whereas 2 presented a pattern of cross-reactivity (Table IV). Of the 7 subjects of group C, 6 had positive responses only to the responsible compound (5 to cefazolin and 1 to cefamandole), and the remaining

TABLE III. Allergologic test results of the 32 subjects of group A with a pattern of cross-reactivity

Subject no.	Sex	Age (y)	Drug involved	Type of reaction	Skin tests				
					CX	CT	CP	CU	CZ
4	14	M	Ceftriaxone	An	+	+	−	−	−
6	67	F	Cefotaxime	An	+	+	−	+	−
9	47	F	Ceftriaxone	An	+	+	−	+	−
			Ceftriaxone	U					
19	49	F	Ceftriaxone	An	+	+	+	+	+
21	58	F	Ceftriaxone	An	+	+	−	−	−
27	59	F	Ceftriaxone	An	+	+	−	−	−
28	44	F	Ceftriaxone	An	+	+	+	+	+
31	54	F	Ceftriaxone	An	+	+	−	+	−
33	69	F	Ceftriaxone	An	+	+	+	+	−
36	68	M	Ceftriaxone	An	+	+	+	−	−
39	66	F	Ceftriaxone	An	+	+	−	−	−
40	26	M	Ceftriaxone	An	+	+	+	−	+
43	45	F	Ceftriaxone	An	+	+	+	−	−
44	74	M	Ceftriaxone	An	+	+	+	−	−
51	81	F	Ceftriaxone	An	+	+	+	−	−
53	71	F	Ceftriaxone	An	+	+	+	+	−
64	16	F	Ceftriaxone	An	−	+	−	+	−
67	60	F	Cefuroxime axetil	An	+	+	+	+	−
70	66	F	Ceftriaxone	An	+	+	+	−	−
73	77	F	Cefotaxime	An	+	−	−	+	−
76	54	F	Ceftriaxone	An	+	+	−	−	−
78	47	F	Ceftriaxone	An	+	+	−	−	−
79	55	F	Cefuroxime	An	+	−	−	+	−
82	66	F	Ceftriaxone	An	+	+	+	−	−
			Ceftazidime	E					
83	19	M	Ceftriaxone	An	−	+	+	+	−
88	65	F	Ceftriaxone	An	+	+	−	−	−
89	53	F	Ceftriaxone	An	+	+	+	−	−
92*	52	F	Cefodizime	An	+	−	−	+	−
94	59	F	Ceftriaxone	An	+	+	−	−	−
96	68	F	Ceftriaxone	An	+	+	+	+	−
100	51	F	Ceftriaxone	An	+	+	−	−	−
101	50	M	Ceftriaxone	U	+	+	+	+	−

An, Anaphylaxis; *CP*, cefepime; *CT*, ceftriaxone; *CU*, cefuroxime; *CX*, cefotaxime; *CZ*, ceftazidime; *E*, erythema; *F*, female; *M*, male; *U*, urticaria.
*This subject had a positive skin test response also to cefodizime.

subject, who had reacted to cefoperazone, had positive responses to both cefoperazone and cefamandole (Table IV, subject 5). The patterns of allergologic test positivity of group D are shown in Table IV.

Excluding one subject who had 2 distinct reactions to cefotaxime and cefazolin (Table IV, subject 56), of the remaining 79 participants who had reacted to group A cephalosporins, 36 (45.5% [95% CI, 35% to 56.5%]) had positive skin test responses to at least 1 other such cephalosporin versus none (0% [95% CI, 0.1% to 14.8%]) of the 22 subjects who had reacted to cephalosporins other than those of group A ($P < .05$, Fisher exact test). Moreover, of the 79 subjects who had reacted to group A cephalosporins, 6 (7.6% [95% CI, 3.6% to 15.6%]) had positive responses to cephalosporins other than the latter, such as cefaclor, cefamandole, and ceftibuten (Table IV, subjects 23, 47, 50, 57, 81, and 102), one of them only in the ImmunoCAP (subject 57).

Of the 15 subjects who reacted to group B cephalosporins, 4 (26.6% [95% CI, 11% to 52.4%]) had positive skin test responses to at least 1 other aminocephalosporin (Table IV, subjects 1, 12, 18, and 25), whereas of the 87 subjects who had reacted to cephalosporins other than those of group B, 5 (5.7% [95% CI, 2.5% to 12.7%]) had positive responses to allergologic tests with at least 1 group B cephalosporin (Table IV, subjects 23, 47, 50, 57, and 81; $P < .05$, Fisher exact test). Two (13.3% [95% CI, 4% to 38.3%]) of the 15 subjects who had reacted to aminocephalosporins also had positive responses to a cephalosporin other than the latter (Table IV, subjects 1 and 25).

Excluding subject 56, of the 7 subjects who had reacted to group C cephalosporins, only 1 (14.3% [95% CI, 3.2% to 52.6%]) had a positive skin test response to another cephalosporin of this group (Table IV, subject 5), whereas of the 94 subjects who had reacted to cephalosporins of group A or B, 5 (5.3% [95% CI, 2.3% to 11.8%]; Table IV, subjects 1, 23, 25, 81, and 102) had positive skin test responses to a group C cephalosporin, specifically to cefamandole and ceftibuten ($P = .3$, Fisher exact test). None of the 7 subjects who had reacted to group C cephalosporins also had a positive response to a cephalosporin of group A or B.

After reacting to a cephalosporin of group A, the estimated relative risk ratio of cross-reacting with at least 1 other cephalosporin of the same group was 21 (95% CI, 1.34-328.95; $P < .05$) and with at least 1 cephalosporin other than those of group A was 0.33 (95% CI, 0.11-0.99; $P < .05$). After reacting to a cephalosporin other than those of group A, the estimated relative risk ratio of cross-reacting with at least 1 group A cephalosporin was 0.05 (95% CI, 0.0-0.75; $P < .05$).

TABLE IV. Allergologic test results of the 12 subjects of groups B, C, and D with a pattern of cross-reactivity

Group	Subject no.	Sex	Age (y)	Drug involved	Type of reaction	CAP-FEIA	Skin tests										
						CE	CE	CT	CH	CM	CU	CX	CP	CD	CZ	CL	CB
B	12	M	14	Cefaclor	An	−	+	−	+	−	−	−	−	−	−	−	−
B	18	F	17	Cefaclor	An	1.17	+	−	+	−	−	−	−	−	−	−	−
C	5*	F	62	Cefoperazone	An	−	−	−	−	+	−	−	−	−	−	−	−
D	1	F	50	Cephalexin	An	−	+	−	+	+	−	−	−	−	−	−	−
D	23	F	51	Ceftriaxone	An	−	+	+	−	+	+	+	+	−	−	−	−
D	25	F	14	Cefaclor	An	−	+	−	+	+	−	−	−	+	−	−	−
D	47	M	72	Ceftriaxone Ceftazidime	An An	−	+	+	−	−	−	−	−	−	−	−	−
D	50	F	55	Cefuroxime axetil	An	−	+	−	+	−	+	+	−	−	−	−	−
D	56	M	39	Cefotaxime Cefazolin	An An	−	−	+	−	−	+	+	+	−	+	+	−
D	57	F	50	Ceftriaxone	An	11.7	−	+	−	−	−	−	−	−	−	−	−
D	81	F	77	Ceftriaxone	An	1.47	−	+	−	+	−	−	−	−	−	−	−
D	102	F	44	Ceftriaxone	An	−	−	+	−	−	+	+	+	−	−	−	+

Subjects 1, 12, 18, and 25 tolerated challenges with cefuroxime axetil, ceftriaxone, cefazolin, and ceftibuten; subject 5 tolerated challenges with cefaclor, cefuroxime axetil, ceftriaxone, cefazolin, and ceftibuten; subjects 23, 47, 50, 57, and 81 tolerated challenges with cefazolin and ceftibuten; subject 56 tolerated challenges with cefaclor and ceftibuten; and subject 102 tolerated challenges with cefaclor and cefazolin.

An, Anaphylaxis; *CB*, ceftibuten; *CD*, cefadroxil; *CE*, cefaclor; *CH*, cephalexin; *CL*, cefazolin; *CM*, cefamandole; *CP*, cefepime; *CT*, ceftriaxone; *CU*, cefuroxime; *CX*, cefotaxime; *CZ*, ceftazidime; *F*, female; *M*, male.

*This subject had a positive skin test response also to cefoperazone.

After reacting to a cephalosporin of group B, the estimated relative risk ratio of cross-reacting with at least 1 other cephalosporin of the same group was 4.64 (95% CI, 1.4-15.33; $P < .05$) and with at least 1 cephalosporin other than those of group B was 0.31 (95% CI, 0.08-1.17; $P < .05$). After reacting to a cephalosporin other than those of group B, the estimated relative risk ratio of cross-reacting with at least 1 group B cephalosporin was 0.22 (95% CI, 0.07-0.71; $P < .05$).

After reacting to a cephalosporin of group C, the estimated relative risk ratio of cross-reacting with at least 1 other cephalosporin of the same group was 2.69 (95% CI, 0.36-19.95; $P = .36$) and with at least 1 cephalosporin other than those of group C was 0.14 (95% CI, 0.01-2.06; $P < .05$). After reacting to a cephalosporin other than those of group C, the estimated relative risk ratio of cross-reacting with at least 1 group C cephalosporin was 0.37 (95% CI, 0.04-2.77; $P = .33$).

Challenges with alternative cephalosporins (ceftibuten in 101, cefazolin in 96, cefaclor in 82, and cefuroxime axetil and ceftriaxone in 22 subjects) were well tolerated.

DISCUSSION

Our data, as well as those in the literature,[9,11-17] indicate that the IgE-mediated response to cephalosporins is heterogeneous and that different patterns of allergologic test positivity can be detected.

As far as the 20 subjects with positive responses to both cephalosporins and penicillin reagents are concerned, in the 7 who reacted to cefaclor or cephalexin, such positive responses can be explained by the fact that these aminocephalosporins share identical R1 side chains with ampicillin (see Fig E2 in this article's Online Repository at www.jacionline.org). However, the remaining 13 subjects had reacted to ceftriaxone or ceftazidime, which have side-chain structures different from those of penicillins, suggesting that coexisting sensitivities can occur, as previously observed both in subjects with penicillin allergy[37] and those with cephalosporin allergy.[14]

With regard to subjects with positive responses to different cephalosporins, including those responsible, the present study confirms that cross-reactivity among cephalosporins is connected mainly with R1 side-chain structures. Specifically, cefuroxime, ceftriaxone, cefotaxime, and cefodizime share a methoxyimino group in their R1 side chains (see Fig E1),[38,39] and cross-reactivity among these drugs has been observed.[11,12,16,17,40] Moreover, ceftriaxone and cefotaxime have an identical R1 side chain (see Fig E1). Ceftazidime has an R1 side chain that is slightly different from those of the aforementioned cephalosporins. The ceftazidime R1 side chain has an alkoxyimino group that has greater steric hindrance than the methoxyimino moiety and therefore would not be expected to be recognized by the same IgE molecules (see Fig E1).[38] Consistent with this, one study found a significant degree of cross-reactivity between cefotaxime and ceftriaxone (odds ratio, 7.0; 95% CI, 2-24) but not between these 2 cephalosporins and ceftazidime.[40] However, in the present study, as well as in some previous studies,[11,14,16,17] there were subjects who had experienced immediate hypersensitivity reactions to ceftazidime, as well as to cefotaxime, ceftriaxone, or both in separate episodes, and displayed positive results on allergologic tests with the responsible compounds. Moreover, in this and previous studies,[11,12,14,16,17] there were participants who had reacted to cephalosporins, such as cefuroxime, ceftriaxone, and cefotaxime, showing positive results in allergologic tests with the responsible compounds, as well as with other group A cephalosporins, including ceftazidime. Therefore cross-reactivity among these cephalosporins seems to be possible as well.

The cross-reactivity between cefaclor and cephalexin found in 4 subjects of the present study who had reacted to these aminocephalosporins is also connected with their R1 side chains, which are identical (see Fig E2). In only one subject who had reacted to cefoperazone did cross-reactivity with cefamandole appear to be related to their identical R2 side chains, which include an N-methyl-tetrazole-thiol group (see Fig E2).

With regard to subjects with positive responses only to the responsible cephalosporin, the subjects' reactivity could have

been to the entire cephalosporin molecule, as previously demonstrated *in vitro* with cefaclor.[41] In the present study cefaclor ImmunoCAP proved to be less sensitive than skin tests. In effect, responses were positive in only 6 of the 12 participants who had reacted to cefaclor and had positive skin test responses. However, cefaclor ImmunoCAP results were positive in 2 subjects who had reacted to ceftriaxone and had positive skin test responses to ceftriaxone and negative responses to cefaclor (Table IV).

Our 102 participants tolerated all 326 challenges with alternative cephalosporins, thus confirming the results of previous reports of small numbers of subjects with IgE-mediated hypersensitivity to cephalosporins who tolerated alternative cephalosporins found to elicit negative skin test responses.[15,18-31]

In the present study all 73 subjects belonging to group A tolerated cefaclor, and all 13 subjects of group B tolerated both cefuroxime axetil and ceftriaxone. Moreover, both group A and B subjects tolerated cefazolin and ceftibuten. We selected these 2 cephalosporins as alternative compounds in subjects of group A and B because they have side chains different from those of the cephalosporins found to elicit positive responses in such subjects. In effect, in previous reports concerning a total of 15 subjects with IgE-mediated reactions to cefazolin,[15,18,20,31,42] 14 displayed selective responses to skin tests with the responsible compound; 7 of the latter underwent challenges with alternative cephalosporins, such as cefaclor, cefuroxime, and ceftriaxone, and tolerated them. Ceftibuten seems to be rarely responsible for IgE-mediated reactions.[28]

All this demonstrates the usefulness of considering side-chain groups when selecting an alternative cephalosporin in subjects with IgE-mediated hypersensitivity to these β-lactams. However, subjects of group D displayed different patterns of positivity, which cannot be explained by either similar or identical side chains or by the common β-lactam ring. Therefore in these cases coexisting sensitivities cannot be excluded.

In this study, as in a previous study assessing subjects with an IgE-mediated hypersensitivity to penicillins,[37] negative cephalosporin skin test responses indicate tolerability. In effect, no adverse reactions to cephalosporins occurred in the 102 subjects of the present study or in the 101 subjects with penicillin allergy of the aforementioned earlier study,[37] who underwent challenges with cefuroxime axetil and ceftriaxone.

However, the present study has some limitations. Even though skin tests with cephalosporins have been used in numerous studies, their positive and negative predictive values are not fully established.[4,5,7,8] Another important limitation of our study is that challenges were not followed by full therapeutic courses because we studied our subjects for research purposes rather than for clinical indications for cephalosporin treatment.

In conclusion, our data indicate that cephalosporin hypersensitivity is unlikely to be a class hypersensitivity. In effect, they allowed us to identify 2 groups (or subclasses) of cephalosporins: group A, which includes those with a methoxyimino group in their R1 side chains plus ceftazidime, and group B, which is composed of aminocephalosporins. The limited number of subjects sensitive to cephalosporins other than those belonging to the aforementioned groups did not allow us to identify further groups.

Moreover, our data provide significant clinical support to the conclusion of the Joint Task Force on Practice Parameters regarding the management of subjects with histories of immediate reactions to cephalosporins who require an alternative cephalosporin.[7] In accordance with such parameters,[7] these subjects can be treated with cephalosporins with dissimilar side chains. However, the present study demonstrated that in subjects with an IgE-mediated hypersensitivity to cephalosporins, the risk of positive allergologic test responses with alternative cephalosporins is not related only to the structural similarities among their side-chain determinants. For this reason, pretreatment skin tests with alternative cephalosporins are advisable before their administration through graded challenges to subjects with cephalosporin allergy.

Clinical implications: Subjects with cephalosporin allergy might be treated with alternative cephalosporins, which have side-chain determinants different from those of the responsible compounds and elicit negative pretreatment skin test responses.

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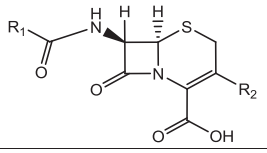
Cephalosporins			
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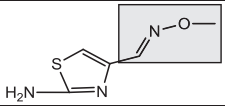
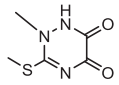
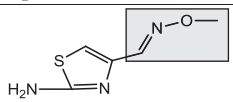
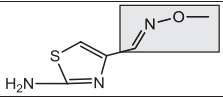
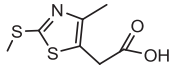
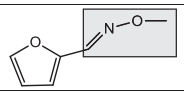
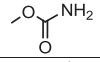
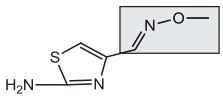
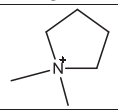
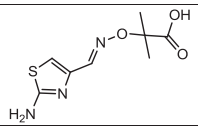
Group A cephalosporins	**Ceftriaxone**		
	Cefotaxime		
	Cefodizime		
	Cefuroxime		
	Cefepime		
	Ceftazidime		

FIG E1. Chemical structures of cephalosporins of group A, with the common methoxyimino group highlighted in *gray*.

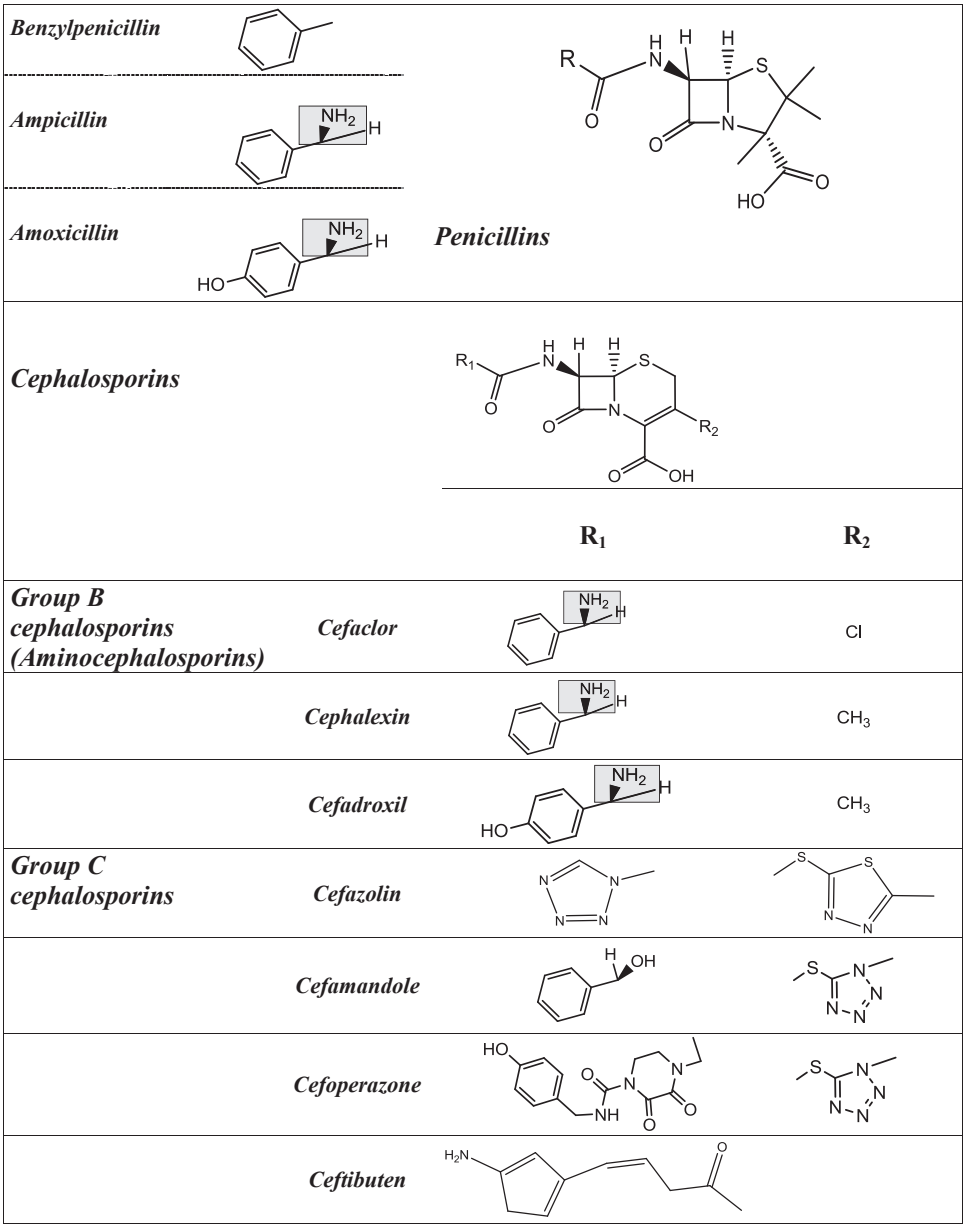


FIG E2. Chemical structures of penicillins, cephalosporins of group B (with the common amino group highlighted in *gray*), and cephalosporins of group C.

TABLE E1. Allergologic test results of the 102 subjects with cephalosporin allergy

	No. (%) of subjects
Positive skin test results to β-lactams, no. (%)	
Penicilloyl-polylysine	4 (3.9)
Minor determinant mixture	3 (2.9)
Benzylpenicillin	6 (5.9)
Ampicillin	4 (3.9)
Amoxicillin	5 (4.9)
Cephalexin	7 (6.9)
Cefaclor	16 (15.7)
Cefadroxil	1 (0.9)
Cefamandole	6 (5.9)
Ceftazidime	11 (10.8)
Ceftriaxone	66 (64.7)
Cefuroxime	19 (18.6)
Cefotaxime	35 (34.3)
Cefepime	19 (18.6)
Cefazolin	6 (5.9)
Ceftibuten	1 (0.9)
Positive specific IgE assay results, no. (%)	
Penicilloyl G	8 (7.8)
Penicilloyl V	10 (9.8)
Ampicilloyl	8 (7.8)
Amoxicilloyl	4 (3.9)
Cefaclor	8 (7.8)