

# Immediate allergic reactions to cephalosporins: Cross-reactivity and selective responses

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**Background:** After penicillins, cephalosporins are the most important  $\beta$ -lactams inducing IgE-mediated reactions. Responses may be selective or cross-reactive with common  $\beta$ -lactam determinants. Unlike determinants derived from benzylpenicillin, cephalosporin allergenic determinants have not been properly identified, even though a wide variety of these  $\beta$ -lactams is currently used.

**Objective:** We sought to evaluate the IgE response in subjects with immediate allergic reactions to injectable cephalosporins and to assess their reactivity to different penicillins and cephalosporins.

**Methods:** We studied 30 subjects with immediate reactions to one or more of the following cephalosporins: ceftriaxone, cefotaxime, ceftazidime, and cefuroxime. Skin tests and in vitro-specific IgE antibody assays were performed for major and minor determinants of penicillin G, amoxicillin, and ampicillin, as well as for the culprit cephalosporins. Responses to cephalosporins other than the culprit ones were also studied by using skin testing.

**Results:** Twenty-six patients (group A, 86.7%) displayed skin test and RAST negativity to penicillin determinants and skin test positivity to cephalosporins, with RAST confirmation in 9 patients. Four subjects (group B, 13.3%) had a positive response to penicillin determinants. In group A two patterns of reactivity were observed: one characterized by a response only to the culprit cephalosporin ( $n = 15$ , 57.7%) and the other by positive responses to different cephalosporins, including the responsible cephalosporins ( $n = 11$ , 42.3%).

**Conclusion:** Most patients with a history of immediate reactions to cephalosporins are sensitized to determinants generated only by cephalosporins (group A), although a small percentage react to penicillin determinants (group B). Some patients from group A responded only to the culprit cephalosporin, but others reacted to different cephalosporins. These findings can be explained in terms of either selective response to unique determinants or cross-reactivity. (*J Allergy Clin Immunol* 2000;106:1177-83.)

**Key words:** Allergy, penicillins, cephalosporins, IgE response, and cross-reactivity

$\beta$ -Lactams are the most important cause of adverse drug reactions mediated by an immunologic mechanism.<sup>1,2</sup> The use of new compounds has resulted in new specific forms of sensitization that may induce allergic reactions.<sup>3</sup> Of all the  $\beta$ -lactams, penicillins are the most frequently involved and the best studied so far,<sup>2,4</sup> possibly because of the higher consumption of these drugs<sup>3</sup> and the stability of the conjugates formed by their derivatives.<sup>5,6</sup> The major antigenic determinant of benzylpenicillin is benzylpenicilloyl, which is formed by the nucleophilic attack of the penicillin molecule by the amino group of proteins found either in plasma or cell membranes.<sup>1,5,6</sup>

Although the equivalent determinant, the cephalosporoyl, may be formed likewise with cephalosporins,<sup>7</sup> less is known about the immunologic response to such structures.<sup>1</sup> In penicillins the whole bicyclic structure remains after benzylpenicilloyl formation, whereas in cephalosporins important changes occur that produce a wide variety of different metabolites.<sup>1,7</sup> This explains the differences in the stability and immunogenicity of the haptenic structures formed. The production of hybridomas has shown that, in addition to common determinants, cephalosporins can generate unique structures capable of inducing a specific immunologic response not cross-reacting with classic structures.<sup>8</sup> Thus allergic reactions to cephalosporins may occur because of sensitization to determinants shared with penicillins or to unique cephalosporin haptens.<sup>4,9,10</sup>

Because the exact haptenic determinants of cephalosporins produced by their degradation are largely unknown, the free individual drugs are used as skin test agents to detect IgE antibodies reactive to these antibiotics.<sup>2,10</sup>

In this study we assessed a group of Italian subjects who had immediate allergic reactions to one or more of 4 injectable cephalosporins diagnosed on the basis of skin test positivity, RAST positivity, or both to penicillin determinants and/or skin test positivity to the culprit cephalosporins. We grouped these subjects into different categories according to their responses to classic penicillins, as well as to cephalosporins other than the responsible ones.

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**TABLE I.** Clinical data of the patients included in the study

Patient No.	Age (y)	Sex	Drug involved	Clinical reaction	Time*
1	6	M	Ceftriaxone	Urticaria	24
2	7	F	Ceftriaxone	Anaphylactic shock	3
3	48	F	Ceftazidime	Urticaria-angioedema	15
4	70	M	Ceftriaxone	Urticaria-angioedema	12
			Ceftazidime	Anaphylactic shock	2
			Cefotaxime	Urticaria-angioedema	1
5	35	F	Ceftazidime	Anaphylactic shock	2
6	24	M	Cefotaxime	Anaphylactic shock	12
7	27	M	Cefotaxime	Anaphylactic shock	2
8	31	F	Ceftriaxone	Anaphylactic shock	1
9	66	F	Cefotaxime	Anaphylactic shock	24
			Ceftazidime	Urticaria	18
10	34	F	Ceftazidime	Urticaria	12
11	57	F	Cefuroxime	Anaphylactic shock	1
12	38	M	Ceftriaxone	Anaphylactic shock	4
13	14	M	Ceftriaxone	Anaphylactic shock	2
14	25	F	Cefotaxime	Anaphylactic shock	3
15	53	F	Cefuroxime	Anaphylactic shock	12
16	63	F	Cefotaxime	Anaphylactic shock	12
17	12	F	Ceftriaxone	Anaphylactic shock	3
18	35	F	Ceftriaxone	Urticaria-angioedema	2
19	72	F	Ceftriaxone	Anaphylactic shock	9
20	63	F	Cefuroxime	Anaphylactic shock	7
21	5	F	Ceftriaxone	Anaphylactic shock	32
22	24	M	Ceftazidime	Anaphylactic shock	2
23	63	M	Cefuroxime	Anaphylactic shock	5
			Cefotaxime	Urticaria-angioedema	2
24	64	F	Ceftriaxone	Anaphylactic shock	45
			Cefotaxime	Anaphylactic shock	40
			Ampicillin	Anaphylactic shock	36
25	49	M	Ceftazidime	Urticaria-angioedema	48
26	35	F	Ceftriaxone	Urticaria-angioedema	24
27	9	F	Ceftriaxone	Anaphylactic shock	4
28	29	F	Ceftriaxone	Urticaria-angioedema	1
29	79	F	Ceftriaxone	Anaphylactic shock	16
30	67	F	Cefotaxime	Anaphylactic shock	7

\*Months elapsed between the last adverse reaction and allergologic evaluation.

## METHODS

### Patient selection

Subjects were selected from a large outpatient Italian population with a history of immediate reactions to injectable cephalosporins and positive results in allergologic evaluations performed between January 1995 and June 1998. We first evaluated the possible existence of allergy to penicillins by using skin tests and RASTs. Allergy to cephalosporin derivatives was evaluated by using skin tests to different cephalosporin compounds, including the culprit drug. In vitro-specific cephalosporin IgE antibodies were determined by using RASTs.

### Skin tests

Prick and intradermal tests were carried out with penicilloylpolylysine (Allergopharma Merck, Reinbeck, Germany), minor determinant mixture (Allergopharma), penicillin G (Pharmacia, Milan, Italy), ampicillin (Amplital, Pharmacia), and amoxicillin (SmithKline Beecham, Milan, Italy). The final concentrations were  $5 \times 10^{-5}$  mmol/L for penicilloylpolylysine,  $2 \times 10^{-2}$  mmol/L for minor determinant mixture, 10,000 IU/mL for penicillin G, and 20 mg/mL for ampicillin and amoxicillin; the last 3 were diluted in 0.9% NaCl.

Cephalothin (Keflin; Lilly, Sesto Fiorentino, Italy), cefamandole

(Mandokef, Lilly), cefuroxime (Curoxim; Glaxo, Verona, Italy), ceftazidime (Glazidim, Glaxo), cefotaxime (Zariviz; Hoechst Roussel, Milan, Italy), and ceftriaxone (Rocefin; Roche, Basel, Switzerland) at a concentration of 2 mg/mL in 0.9% NaCl were also used.

All of the above reagents were initially tested on the volar forearm skin by using the prick method, and reactions were considered positive when a wheal of greater than 3 mm in diameter was present 20 minutes later. When prick test responses were negative, 0.01 mL of the reagent solution was injected intradermally on volar forearm skin. Readings were made 20 minutes after injection. Results were considered positive when wheals of greater than 5 mm were present. Positive controls for prick and intradermal tests were done with histamine (at 10 and 1 mg/mL, respectively). Normal saline was used as a negative control. The concentration used for cephalosporins had proved to be a nonirritant in a control group of 40 healthy subjects, as previously described.<sup>11</sup>

To minimize the risk of systemic reactions to skin testing, when histories were strongly positive, the dilution was started at concentrations from 1000 to 10 times lower than that stated above.

### Specific IgE antibodies

These were made by RAST to benzylpenicilloyl-polylysine, amoxicilloyl-polylysine, and ampicilloyl-polylysine, as previously

**TABLE II.** In vivo and in vitro studies with penicillin determinants

Patient No.	In vivo tests					In vitro tests		
	PPL	MDM	PG	AX	AMP	BPO-PLL	AX-PLL	AMP-PLL
1	-	-	-	-	-	0	0	0.2
2	-	-	-	-	-	0.1	0	0.3
3	-	-	-	-	-	0	0	0.2
4	-	-	-	-	-	1.0	0.1	0.4
5	-	-	-	-	-	0.7	0.7	<b>2.9</b>
6	-	-	-	-	-	0	0	0
7	-	-	-	-	-	0.2	0.5	0.1
8	-	-	-	-	-	0	0.1	0
9	-	-	-	-	-	0.1	0.9	0.4
10	-	-	-	-	-	0	0	0
11	-	-	-	-	-	0.7	0.7	0
12	-	-	-	-	-	2.2	2.2	<b>3.3</b>
13	-	-	-	-	-	0.1	0	0.1
14	-	-	-	-	-	0.1	0.3	0.2
15	-	-	-	-	-	0	0	0
16	-	-	-	-	-	0.1	0.3	0
17	-	-	-	-	-	0	0	0
18	-	-	-	-	-	0	0.1	0.1
19	-	-	-	-	-	0.1	0.1	0.3
20	+	-	-	-	-	<b>10.7</b>	0	0
21	-	-	-	-	-	0	0.1	0.1
22	-	-	-	-	-	0	0.1	0
23	-	-	-	-	-	0.1	0	0
24	+	-	-	-	-	2.3	0.2	0.2
25	-	-	-	-	-	0.2	0	0
26	-	-	-	-	-	0.7	0.6	0.3
27	-	-	-	-	-	0.9	0.7	0.5
28	-	-	-	-	-	0.9	0.7	0.3
29	-	-	-	-	-	0	0	0.1
30	-	-	-	-	-	0.1	0	0

Bold numbers correspond to positive results (over cutoff values).

PPL, Penicilloylpolylysine; MDM, minor determinant mixture; PG, penicillin G; AX, amoxicillin; AMP, ampicillin; BPO-PLL, benzylpenicilloyl-polylysine; AX-PLL, amoxicilloyl-polylysine; AMP-PLL, ampicilloyl-polylysine.

described.<sup>12</sup> Assays were also performed with the responsible cephalosporin conjugated to polylysine (Sigma, St Louis, Mo) with the same methodology used for penicillins. Blood samples were obtained when patients were evaluated, and sera were kept at -20°C until assayed. All samples were made in parallel, and values were considered positive if they were higher than 2.5% of label uptake, which was the mean +2 SD of the negative control group with total IgE ranging from 8 to 1300 kU/L.<sup>13</sup>

## RESULTS

A total of 30 patients (11 male and 19 female patients) were included in the study. The mean age was 40 years, ranging from 5 to 79 years. Our work-up was performed with a time interval of 12.36 ± 13.4 months (range, 1-48 months) after the most recent adverse reaction. Clinical data are shown in Table I. In all patients the time between drug administration and the onset of symptoms was less than 1 hour. The patients had a total of 25 episodes of anaphylactic shock and 11 episodes of urticaria with or without angioedema. Anaphylactic shock ranged from mild to severe, and in 2 patients there was respiratory arrest.

The responsible compounds were ceftriaxone (reactions in 15 patients), followed by cefotaxime (9 patients),

ceftazidime (7 patients), and cefuroxime (4 patients). Urticaria was induced in 5 patients by using ceftriaxone, in 4 by using ceftazidime, in 2 by using cefotaxime, and in none by using cefuroxime. Anaphylactic shock was provoked in 10 subjects by using ceftriaxone, in 7 by using cefotaxime, in 4 by using cefuroxime, in 3 by using ceftazidime, and in 1 by using ampicillin.

The majority (26 patients) had only one episode induced by a cephalosporin, whereas in 4 subjects (patients 4, 9, 23 and 24) reactions to different β-lactams in separate episodes had occurred (Table I).

Skin test results, RAST results, or both were positive for one or more penicillin determinants in 4 patients. Patients 20 and 24 had positive skin test responses to penicilloylpolylysine, with RAST positivity in the former; patients 5 and 12 displayed only RAST positivity to ampicilloyl-polylysine (Table II).

With regard to the skin test results for the cephalosporins studied, a total of 32 positive reactions were observed: 9 were determined by using prick testing and 23 by using intradermal tests (Table III). As far as cephalosporin RASTs are concerned, 9 patients had positive responses to the culprit cephalosporins (1 to cefo-

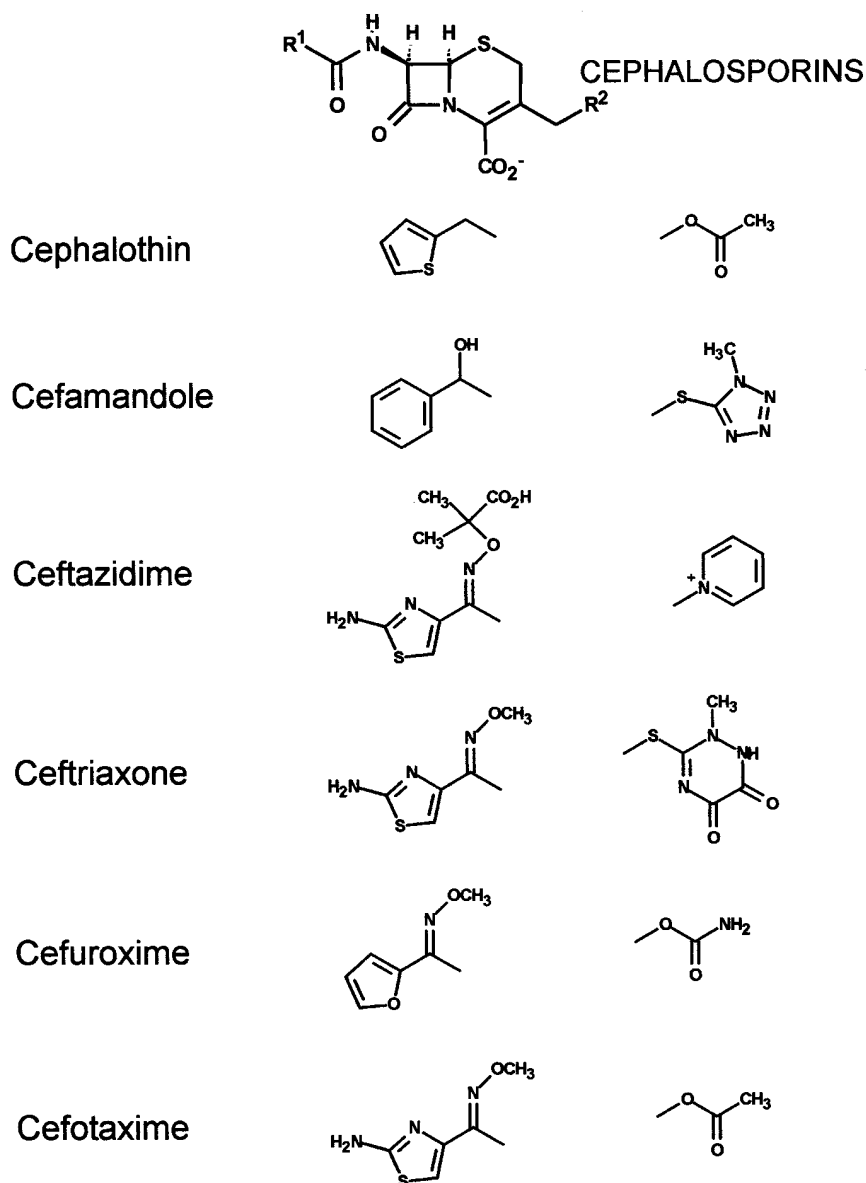


FIG 1. Chemical structures of the cephalosporins used for skin testing.

taxime, 4 to cefuroxime, and 4 to ceftriaxone). No patients had positive RAST and negative skin test responses (Table III). It is interesting to note that patient 24, who had reacted to ceftriaxone, cefotaxime, and ampicillin in separate episodes, had negative skin test and RAST responses to the culprit drugs and displayed only skin test positivity to penicilloypolylysine.

Patients were then classified into 2 groups: those with positive results only to cephalosporin determinants (group A) and those with positive results to penicillin determinants (group B). Of all the patients evaluated, 4 (13.3%) belonged to group B, and 26 (86.7%) belonged to group A.

In group A, on the basis of skin testing with a panel of first-, second-, and third-generation cephalosporins, two

patterns of reactivity were observed (Table IV): one characterized by responses only to culprit cephalosporins ( $n = 15$ , 57.7%) and the other by positive responses to different cephalosporins, including the responsible ones ( $n = 11$ , 42.3%). Patient 9, who had experienced adverse reactions to cefotaxime and ceftazidime, was included in the latter group, even though he displayed skin test positivity only to ceftazidime.

The chemical structures of the cephalosporins used for skin testing are shown in Fig 1. Among patients who had experienced adverse reactions to ceftriaxone, selective responses to this drug were found in 9 patients (patients 1, 2, 8, 17, 18, 19, 21, 27, and 29). In two patients (patients 13 and 28) there was cross-reactivity with cefotaxime, which has the same  $R_1$  side chain as ceftriaxone;

in another patient (patient 26) there was cross-reactivity with cefotaxime and cefuroxime, which have similar side-chain structures.

With regard to the rest of the cephalosporins, the differences between selective and cross-reactive responses were not so clear. Patients who had reacted to ceftazidime displayed selective skin test responses in 3 patients (patients 3, 10, and 25), and in patient 22 there was cross-reactivity with ceftriaxone, cefotaxime, and cefuroxime. Among the patients who had reacted to cefotaxime, there were two selective responses (patients 7 and 16) and 3 cross-reactive responses: patient 6 with ceftriaxone and cefuroxime, patient 14 with cefuroxime, and patient 30 with ceftriaxone. When cefuroxime was the culprit drug, one patient (patient 11) had a selective response, and another (patient 15) displayed cross-reactivity with different cephalosporins, including cephalothin.

Finally, subjects in group A who had experienced adverse reactions to different cephalosporins in separate episodes (patients 4, 9, and 23) had positive responses to several cephalosporins, including the culprit responses, except patient 9, as previously described.

## DISCUSSION

Most studies of  $\beta$ -lactam allergy have been based on responses to penicillin or its derivatives.<sup>1,2,4</sup> Furthermore, in studies of cross-reactivity between penicillins and cephalosporins, the subjects were originally sensitized to penicillins and cross-reactivity with cephalosporins was assessed by testing one or two compounds of the latter.<sup>1,14-18</sup> Few studies have been carried out to evaluate cross-reactivity with penicillin or other  $\beta$ -lactams in subjects with primary hypersensitivity to cephalosporins.<sup>19,20</sup> Experimental studies on identification of cephalosporin epitopes,<sup>8</sup> later confirmed by clinical studies,<sup>20</sup> indicate that there are antibodies that recognize structures unique to cephalosporins, with little or no recognition of penicillins.

One of the major problems for the allergologic evaluation of adverse reactions to cephalosporins is that many of the latter are not available in aqueous solution for therapeutic use, and therefore they require manipulation for both in vivo or in vitro testing. To overcome this difficulty, we only included subjects who had reacted to 4 injectable cephalosporins. IgE-mediated responses to most of these drugs have already been described,<sup>11,20-24</sup> with ceftriaxone and cefuroxime being the most frequently reported in selective reactions.

In the present study we examined the IgE responses in patients with immediate allergic reactions to cephalosporins by performing skin tests and RASTs with the responsible drugs and also assessed the response to other cephalosporins, as well as to classic penicillin determinants. Our sample suggests that a small percentage (<20%) of cephalosporin-allergic subjects react to penicillin determinants (group B), although most have positive results only to cephalosporins (group A). The latter displayed two patterns of skin test reactivity: one charac-

**TABLE III.** In vivo and in vitro studies with cephalosporin determinants

Patient No.	Culprit drug	Skin tests	RAST
1	Ceftriaxone	ID+	0.33
2	Ceftriaxone	ID+	0.42
3	Ceftazidime	ID+	0.06
4	Ceftriaxone	ID+	1.24
	Ceftazidime	P+	0.16
	Cefotaxime	ID+	2.07
5	Ceftazidime	P+	1.23
6	Cefotaxime	ID+	1.24
7	Cefotaxime	ID+	1.01
8	Ceftriaxone	ID+	0.65
9	Cefotaxime	-	0
	Ceftazidime	ID+	0.34
10	Ceftazidime	ID+	0.33
11	Cefuroxime	P+	<b>5.47</b>
12	Ceftriaxone	P+	0.47
13	Ceftriaxone	ID+	<b>2.7</b>
14	Cefotaxime	ID+	0.72
15	Cefuroxime	P+	<b>2.98</b>
16	Cefotaxime	ID+	0.45
17	Ceftriaxone	ID+	1.64
18	Ceftriaxone	ID+	0.45
19	Ceftriaxone	ID+	<b>2.56</b>
20	Cefuroxime	ID+	<b>5.17</b>
21	Ceftriaxone	ID+	0.6
22	Ceftazidime	ID+	0.27
23	Cefuroxime	P+	<b>8.55</b>
	Cefotaxime	ID+	0.93
24	Ceftriaxone	-	0.33
	Cefotaxime	-	1.09
25	Ceftazidime	ID+	0.4
26	Ceftriaxone	ID+	0.2
27	Ceftriaxone	P+	0.7
28	Ceftriaxone	ID+	<b>3.71</b>
29	Ceftriaxone	P+	<b>4.53</b>
30	Cefotaxime	P+	<b>2.8</b>

Bold numbers correspond to positive results (over cutoff values).  
ID+, Intradermal test positivity; P+, prick test positivity.

terized by selective responses to the culprit cephalosporins and the other by positive responses to different cephalosporins. In subjects responding to different cephalosporins, cross-reactivity might be explained by the fact that some drugs, such as ceftriaxone and cefotaxime, have the same side-chain structure, and others, like ceftriaxone and cefuroxime, have a very similar one; moreover, although the ceftazidime side-chain structure is slightly different from the others, a certain cross-reactivity also occurs between this cephalosporin and cefuroxime, cefotaxime, and ceftriaxone.

In those patients from group A with selective responses to culprit cephalosporins, such responses may be explained by the fact that the patients' reactivities could have been with the entire molecule, as previously demonstrated with cefaclor.<sup>9</sup>

In the present study the percentage of subjects who displayed skin test positivity, RAST positivity, or both to penicillin determinants (group B) is much lower than that

TABLE IV. Skin tests with cephalosporins in group A patients

Patient No.	Culprit drug	Cephalosporins					
		CL	CM	CZ	CT	CU	CX
1	Ceftriaxone	-	-	-	+	-	-
2	Ceftriaxone	-	-	-	+	-	-
3	Ceftazidime	-	-	+	-	-	-
4	Ceftriaxone	-	-	+	+	+	+
	Ceftazidime						
	Cefotaxime						
6	Cefotaxime	-	-	-	+	+	+
7	Cefotaxime	-	-	-	-	-	+
8	Ceftriaxone	-	-	-	+	-	-
9	Cefotaxime	-	-	+	-	-	-
	Ceftazidime						
10	Ceftazidime	-	-	+	-	-	-
11	Cefuroxime	-	-	-	-	+	-
13	Ceftriaxone	-	-	-	+	-	+
14	Cefotaxime	-	-	-	-	+	+
15	Cefuroxime	+	-	-	+	+	+
16	Cefotaxime	-	-	-	-	-	+
17	Ceftriaxone	-	-	-	+	-	-
18	Ceftriaxone	-	-	-	+	-	-
19	Ceftriaxone	-	-	-	+	-	-
21	Ceftriaxone	-	-	-	+	-	-
22	Ceftazidime	-	-	+	+	+	+
23	Cefuroxime	-	-	-	+	+	+
	Cefotaxime						
25	Ceftazidime	-	-	+	-	-	-
26	Ceftriaxone	-	-	-	+	+	+
27	Ceftriaxone	-	-	-	+	-	-
28	Ceftriaxone	-	-	-	+	-	+
29	Ceftriaxone	-	-	-	+	-	-
30	Cefotaxime	-	-	-	+	-	+

CL, Cephalothin; CM, cefamandole; CZ, ceftazidime; CT, ceftriaxone; CU, cefuroxime; CX, cefotaxime.

(50%) found in a previous study by our group, which evaluated 12 patients with immediate allergic reactions to different cephalosporins.<sup>20</sup> This could be due to the fact that most of the subjects in the present study had experienced adverse reactions to third-generation and none to first-generation cephalosporins, whereas some patients in the previous study had reacted also to first-generation cephalosporins, whose structural features are more similar to those of penicillin.<sup>25</sup>

RASTs did not show specific IgE in all our subjects. However, due consideration should be given to the fact that cephalosporin allergenic determinants have not been fully identified, and cephalosporin conjugates are reported to be unstable.<sup>26</sup> Furthermore, in some of the patients with negative responses, the assays were performed several months after reactive episodes, and it is possible that the IgE titer had fallen below the cutoff values because the concentration of penicilloyl IgE antibodies is known to decrease with time after an allergic reaction.<sup>27,28</sup> In any case RASTs appear to be less sensitive than skin tests, particularly in subjects with allergic reactions to ceftazidime and cefotaxime.

The question of whether subjects later had a response to cephalosporins because of cross-reactivity with peni-

cillins or because of coexisting sensitivities is difficult to answer. Although after an extensive search, including cross-inhibition studies and challenges, our group has not found any such concomitant sensitivities,<sup>13,20</sup> some authors suggest that coexisting sensitivities may occur.<sup>29</sup>

We did not challenge our patients with  $\beta$ -lactams other than the culprit cephalosporin that were found to induce negative responses in the allergologic work-up. However, many studies assessing the selectivity of the response to a given cephalosporin in single cases indicate that negative results in skin testing with  $\beta$ -lactams other than the responsible cephalosporin are a reliable indicator of tolerability.<sup>21-24</sup> Studies on larger samples are required, however, to allow the routine prescription in patients allergic to cephalosporins of alternative cephalosporins, penicillins, or both selected on the basis of skin test and RAST negativity.

The results of this study show that among subjects with immediate allergic reactions to cephalosporins, 3 main patterns of reactivity are possible. Subjects may present cross-reactivity with determinants of the penicillin group, display reactivity to more than one cephalosporin, or respond only to a culprit cephalosporin. These data sup-

port previous studies of specific responses to nonclassic determinants and show that only a minority of patients seems to respond to common determinants shared with the benzylpenicilloyl group.

Because of current prescription tendencies, it can be expected that this phenomenon will increase, and greater effort should therefore be made to validate new *in vivo* and *in vitro* tests.

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