

BRIEF COMMUNICATION

Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins

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Abstract

There are studies demonstrating that skin-test sensitivity to penicillins can decrease over time and that allergic patients may lose sensitivity if the responsible compounds are avoided. With regard to subjects with IgE-mediated hypersensitivity to cephalosporins, however, such studies are lacking. We evaluated prospectively in a 5-year follow-up 72 cephalosporin-allergic patients. After the first evaluation, patients were classified into two groups according to their patterns of allergologic-test positivity: to both penicillins and cephalosporins (group A), or only to cephalosporins (group B). Skin tests and serum-specific IgE assays were repeated 1 year later and, in case of persistent positivity, 3 and 5 years after the first allergologic examination. Seven (43.7%) of the 16 subjects of group A and 38 (67.8%) of the 56 patients of group B became negative; one was lost to follow-up. Patients of group B became negative sooner and more frequently than group A subjects.

Skin tests with cephalosporins have proved to be useful in diagnosing hypersensitivity reactions to these β -lactams (1–6). In evaluating immediate reactions to β -lactams, the time interval between the last reaction and the allergologic evaluation is crucial for the detection of IgE antibodies in the skin (7, 8). In studies concerning patients with immediate hypersensitivity to penicillins or cephalosporins, skin tests are more likely to be positive the less time has elapsed since the clinical reaction (2, 4, 9, 10).

Moreover, in a few studies concerning the evolution of skin-test positivity to penicillins, up to 50% of patients displayed negative responses 1 year after the initial evaluation (11–14). In addition, another study (15) demonstrated that in penicillin-allergic subjects both the serum-specific IgE assay and the basophil activation test became negative over time. In subjects allergic to cephalosporins, however, these studies are lacking.

In this study, we evaluated prospectively a sample of well-characterized cephalosporin-allergic patients to determine the persistence over time of positivity to skin tests.

Methods

Subjects were recruited prospectively from an outpatient population with histories of immediate reactions to cephalosporins.

To be included in the follow-up study, subjects must have displayed positive skin tests to the responsible cephalosporins; moreover, they must have undergone retesting.

Allergic subjects exposed to cephalosporins, such as health-care workers, pharmacists, veterinarians, and people working in chemical factories, were excluded. In addition, exclusion criteria were pregnancy, use of β -blockers, and severe cardiovascular, renal, or respiratory compromise.

Before the study, a written informed consent was obtained from each patient or the parents of those <18 years of age. The respective institutional review boards approved the protocol.

In the first evaluation, we performed skin tests using penicilloyl-polylysine, minor determinant mixture, benzylpenicillin, ampicillin, amoxicillin, and a panel of cephalosporins, including the responsible ones (Table 1). We also performed serum total and specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor, as previously described (2).

Allergologic tests were repeated 1 year after the first evaluation, and, in case of persistent positivity, also 3 and 5 years after said evaluation.

The evolution of skin-test sensitivity was analyzed by a survival analysis (Kaplan–Meier test using log-rank statistics). Comparisons for quantitative variables without a normal

Table 1 Clinical data of 72 subjects with cephalosporin allergy

	All patients (<i>n</i> = 72)
Age (years), mean (SD)	41.5 (19.9)
Women, <i>n</i> = (%)	50 (69.4)
Time since last cephalosporin reaction*, median (range) [25th, 75th percentile]	3 (1–264) [1, 11]
Family history of allergic disease, <i>n</i> (%)	27 (37.5)
Personal history of allergic disease, <i>n</i> (%)	25 (34.7)
Responsible cephalosporins, <i>n</i> (%)	All reactions (<i>n</i> = 78)
Ceftriaxone	27 (34.6)
Cefotaxime	13 (16.7)
Ceftazidime	11 (14.1)
Cefaclor	10 (12.8)
Cefuroxime	4 (5.1)
Cefatrizine	4 (5.1)
Cefamandole	2 (2.6)
Cefazolin	2 (2.6)
Cefodizime	2 (2.6)
Cephalexin	1 (1.3)
Cefoperazone	1 (1.3)
Cefonicid	1 (1.3)
Manifestation, <i>n</i> (%)	All reactions (<i>n</i> = 78)
Anaphylaxis	64 (82.1)
Urticaria and angioedema	11 (14.1)
Urticaria	3 (3.8)

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

distribution were carried out using the Mann–Whitney and Kruskal–Wallis tests. All reported *P*-values represented two-tailed tests, with values ≤ 0.05 considered statistically significant. The statistical analysis was performed using the SPSS program, version 20 (IBM Corporation, Armonk, NY, USA). To establish the potential determinants of skin-test negativization, we examined the following variables: gender, age at the time of the first evaluation, personal and familiar history of atopy, time interval between the last cephalosporin hypersensitivity reaction and the first allergologic evaluation, clinical reaction type (i.e., anaphylaxis vs urticaria and/or angioedema), culprit drugs, and total serum IgE level (≤ 150 kU/l or >150 kU/l).

Results

We examined 72 subjects who ranged in age from 13 to 80 years and had positive skin tests to at least the responsible cephalosporins.

None of these cases had any exclusion criteria.

The clinical characteristics of the patients enrolled in the study and the drugs responsible for the adverse reactions are presented in Table 1.

After the first evaluation, patients were classified into two groups on the basis of their patterns of positivity: group A (*n* = 16) positive to one or more penicillin reagents

and cephalosporins, and group B (*n* = 56) positive only to cephalosporins. Of these 56 subjects, 22 were positive to different cephalosporins, including the responsible ones (subgroup B1), and 34 were positive only to the culprit cephalosporins (subgroup B2).

The results of skin tests and specific IgE assays of group A, subgroup B1, and subgroup B2 are reported in Tables S1, S2, and S3, respectively.

Overall, of the total of 72 subjects, 49 (68.1%), 36 (50%), and 26 (36.1%) continued to have positive skin-test responses after 1, 3, and 5 years, respectively.

The results of the survival analysis are presented in Fig. 1. Of the 16 subjects of group A, two became negative after 1 year; two others at the 3-year evaluation, and three at the 5-year evaluation.

Among the 56 patients of group B, 21 became negative after 1 year (10 in subgroup B1 and 11 in subgroup B2), 11 were negative at the 3-year evaluation (five in subgroup B1 and six in subgroup B2), and six at the 5-year evaluation (one in subgroup B1 and five in subgroup B2); one was lost to follow-up.

In group A, of the nine patients who maintained test positivity during the entire follow-up period, two (Table S1, patients 2 and 13) remained positive only to penicillin determinants, the remaining seven (Table S1, patients 3, 4, 8, 10, 12, 15, and 16) were positive to both penicillin and cephalosporin reagents, one of them (Table S1, patient 3) only in serum-specific IgE assays.

Of the six patients of subgroup B1 who remained positive to allergologic tests with cephalosporins, four remained positive only to the culprit drugs (Table S2, patients 3, 9, 10, and 15), while two displayed positive responses to different cephalosporins including the responsible ones (Table S2, patients 13 and 20).

Patients of group B became negative sooner and more frequently (long-rank test = 5.60; $P < 0.05$) than those of group A. Patients with a time interval <12 months between the last hypersensitivity reaction and the first allergologic evaluation (group 1, *n* = 55) also became negative sooner and more frequently than patients with a time interval ≥ 12 months (group 2, *n* = 17) (long-rank test = 5.8; $P < 0.05$) (Fig. 1).

Discussion

The present study confirms the results of previous ones (11–14), which followed penicillin-allergic patients by repeating allergologic tests, demonstrating that they may lose their skin-test positivity over time. However, similar studies concerning the evolution of sensitivity to cephalosporins were lacking and to our knowledge this is the first follow-up study of patients allergic to these β -lactams.

We classified our patients according to their patterns of allergologic test positivity. With regard to subgroup B1, the fact that four of the six patients of this subgroup, who remained positive to cephalosporin skin tests, displayed positive responses only to the culprit drug indicates that the selectivity of skin-test responses could be affected by the time interval between the last reaction and allergologic evaluation.

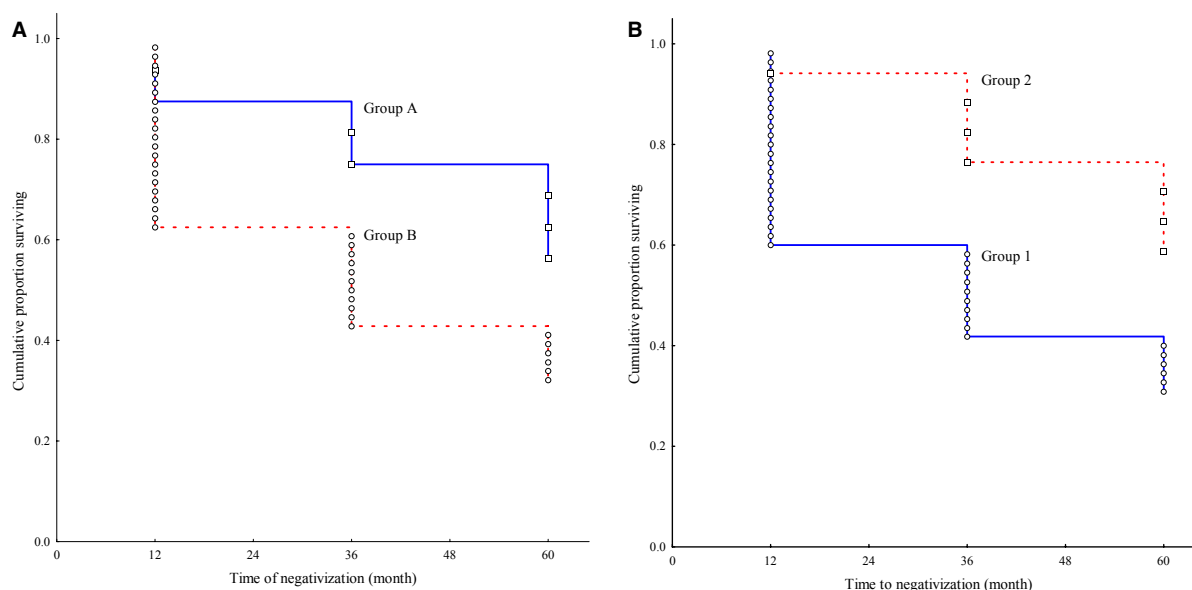


Figure 1 Survival analysis of negativization of skin-test responses in patients with allergologic test positivity to both penicillins and cephalosporins (group A), or only to cephalosporins (group B) and in patients with a time interval <12 months between the last cephalosporin hypersensitivity reaction and the first allergologic evaluation (group 1) and patients with such time interval equal to or more than 12 months (group 2).

Therefore, subjects evaluated more than several months after the reaction might present skin-test responses falsely selective to the responsible drugs. As far as patients of subgroup B2 are concerned, it is noteworthy that, unlike what was observed in the study by Blanca et al. (14)—in which all subjects with selective responses to amoxicillin became negative at the 5-year evaluation—approximately one-third of the patients with selective responses to cephalosporins maintained skin-test sensitivity at the 5-year evaluation.

The results of the present study indicate that more than 60% of subjects with IgE-mediated hypersensitivity to cephalosporins may lose their skin-test positivity over time. For this reason, in the case of immediate reactions to cephalosporins, negative skin-test results should be interpreted in light of the time elapsed since the subject's last exposure to the drug. Therefore, in individuals with immediate reactions to cephalosporins who present negative skin tests when evaluated more than half a year after their reactions, the pathogenic mechanism can be clarified by performing challenges with the suspected cephalosporins and retesting them after 2–4 weeks to exclude a possible resensitization after loss of sensitivity (7, 8).

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Conflicts of interest

All authors have no conflicts of interest to declare.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Allergologic test results of the 16 patients of group A.

Table S2. Allergologic test results of the 22 patients of subgroup B1.

Table S3. Allergologic test results of the 34 patients of subgroup B2.

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Table S1 Allergologic test results of the 16 patients of group A

Patient	Culprit drug	Skin tests												ImmunoCAP				
		PPL	MDM	BP	AM	AX	CULPRIT	CE	CM	CZ	CT	CU	CX	PG	PV	AMy	AXy	CE
1	Cefatrizine	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	.
2	Cefuroxime	+	-	-	-	-	+	-	-	-	-	+	-	-	-	-	-	-
3	Cefaclor	-	-	-	-	-	+	+	-	-	-	-	-	4.49	14.9	0.39	-	2.53
4	Ceftriaxone	-	-	-	-	-	+	-	-	-	+	+	+	8.02	9.27	2.57	-	-
5	Ceftriaxone	-	-	-	-	-	+	-	-	-	+	-	+	0.38	1.67	0.49	-	0.56
6	Cefatrizine	-	-	-	-	-	+	-	-	-	-	-	-	0.49	-	-	-	-
7	Ceftazidime	-	-	-	-	-	+	-	-	+	-	-	-	-	0.40	-	-	-
8	Cefamandole	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-
9	Cefaclor	-	-	-	-	-	+	+	-	-	-	-	-	-	-	2.68	-	-
10	Ceftriaxone	-	-	-	-	-	+	+	+	-	+	+	+	1.62	2.52	0.96	1.02	0.67
11	Ceftriaxone	-	-	-	-	-	+	-	-	-	+	-	-	0.81	0.76	1.19	-	0.47
12	Ceftriaxone	+	+	+	-	-	+	-	-	-	+	-	-	-	-	-	-	-
13	Cefonicid	+	+	-	+	-	+	-	-	-	-	-	-	-	7.98	-	-	-
14	Cefaclor	-	-	+	+	+	+	+	+	-	+	-	+	-	-	-	-	-
15	Ceftazidime	-	-	-	-	-	+	-	-	+	-	-	-	0.63	0.56	-	-	-
16	Cephalexin	+	+	+	+	+	+	+	+	+	+	-	-	0.43	-	-	-	-

AM indicates ampicillin; AMy, ampicilloyl; AX, amoxicillin; AXy, amoxicilloyl; BP, benzylpenicillin; CE, cefaclor; CM, cefamandole; CZ, ceftazidime; CT ceftriaxone; CU, cefuroxime; CX, cefotaxime; MDM, minor determinant mixture; PG, penicilloyl G; PPL, penicilloyl-polylysine; PV, penicilloyl V.

Table S2 Allergologic test results of the 22 patients of subgroup B1

Patient	Culprit drug	Skin tests							Immuno-CAP
		CULPRIT	CE	CM	CZ	CT	CU	CX	CE
1	Ceftriaxone	+	-	-	+	+	+	+	-
2	Ceftriaxone	+	-	-	+	+	+	+	-
3	Ceftriaxone	+	-	-	-	+	-	+	-
4	Cefotaxime	+	-	+	+	+	+	+	-
5	Ceftazidime	+	-	-	+	+	+	-	-
6	Cefotaxime	+	-	-	-	+	+	+	-
	Cefuroxime axetil	+							
7	Cefotaxime	+	-	-	-	+	+	+	-
8	Cefuroxime	+	-	-	-	+	+	+	-
9	Cefotaxime	+	-	-	-	+	+	+	-
10	Cefotaxime	+	-	-	+	+	+	+	-
	Cefazolin	+							
11	Cefodizime	+	-	-	-	+	+	+	-
12	Cefotaxime	+	-	-	+	+	+	+	-
13	Ceftriaxone	+	-	-	-	+	+	+	-
14	Ceftriaxone	+	-	-	-	+	-	+	-
15	Cefoperazone	+	-	+	-	-	-	-	-
16	Ceftriaxone	+	-	-	-	+	+	+	-
17	Cefotaxime	+	-	-	-	+	-	+	-
18	Ceftriaxone	+	-	-	-	+	-	+	-
19	Ceftriaxone	+	-	-	-	+	-	+	-
20	Cefotaxime	+	-	-	+	+	-	+	-
	Ceftazidime	+							
21	Cefotaxime	+	-	-	-	+	+	+	-
22	Cefotaxime	+	-	-	-	+	+	+	-

CE indicates cefaclor; CM, cefamandole; CZ, ceftazidime; CT ceftriaxone; CU, cefuroxime; CX, cefotaxime.

Table S3 Allergologic test results of the 34 patients of subgroup B2

Patient	Culprit drug	Skin tests	ImmunoCAP
			CE
1	Cefotaxime	+	-
2	Cefaclor	+	0.42
3	Ceftazidime	+	-
4	Cefaclor	+	1.16
5	Cefodizime	+	-
6	Ceftazidime	+	-
7	Ceftriaxone	+	-
8	Ceftazidime	+	-
9	Ceftriaxone	+	-
10	Ceftriaxone	+	-
11	Cefatrizine	+	-
12	Ceftriaxone	+	-
13	Ceftazidime	+	-
14	Ceftazidime	+	-
15	Cefazolin	+	-
16	Ceftriaxone	+	-
17	Cefaclor	+	-
18	Ceftriaxone	+	-
19	Ceftriaxone	+	-
20	Ceftriaxone	+	-
21	Ceftazidime	+	-
22	Ceftriaxone	+	-
23	Ceftazidime	+	-
24	Cefotaxime	+	-
25	Cefaclor	+	-
26	Cefuroxime axetil	+	-
27	Cefamandole	+	-
28	Ceftriaxone	+	-
29	Ceftriaxone	+	-
30	Ceftriaxone	+	-
31	Ceftriaxone	+	-
32	Ceftriaxone	+	-
33	Cefaclor	+	-
34	Cefaclor	+	1.17

CE indicates cefaclor.