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Diagnosing Hypersensitivity Reactions to Cephalosporins in Children

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What's Known on This Subject

Cephalosporins may cause hypersensitivity reactions classifiable as immediate or nonimmediate.

What This Study Adds

In children, few nonimmediate manifestations associated with cephalosporin therapy are actually hypersensitivity reactions, whereas most immediate reactions to cephalosporins are IgE-mediated. Cephalosporin skin testing is a useful tool for evaluating such reactions.

ABSTRACT

OBJECTIVES. The goals were to evaluate the usefulness of skin tests, patch tests, serum specific IgE assays, and challenges in diagnosing hypersensitivity reactions to cephalosporins and to clarify the pathogenic mechanism of such reactions.

METHODS. Children with immediate manifestations (within 1 hour) underwent immediate-reading skin tests with penicillin reagents and any suspect cephalosporins, serum specific IgE assays, and challenges; some children underwent reevaluations. Children with nonimmediate manifestations (after >1 hour) were assessed with patch tests, delayed-reading skin tests, and challenges.

RESULTS. We evaluated 148 children with hypersensitivity reactions to cephalosporins, mainly cefaclor and ceftriaxone; 105 had experienced nonimmediate manifestations (mostly urticarial eruptions and maculopapular rashes) and 43 immediate manifestations (anaphylactic shock, urticaria and/or angioedema, and erythema). None of the nonimmediate reactors demonstrated positive results in patch tests and/or delayed skin tests; only 1 subject displayed immediate positive responses to penicillin skin-test reagents. Among the 104 patients with negative results, 96 underwent challenges; 95 tolerated the challenges, and 1 reacted to the cefaclor pediatric suspension and tolerated the challenge with a cefaclor capsule. In the first allergologic evaluation, 33 of the 43 children with immediate reactions displayed skin-test positivity. Of the 10 patients with negative results, 7 underwent challenges, followed by therapeutic courses and reevaluations for 4. All challenges and therapeutic courses were tolerated; in the reevaluation, 1 girl demonstrated positive skin-test results for both the responsible cephalosporin and penicillin reagents. Overall, IgE-mediated hypersensitivity was diagnosed for 34 (79%) of 43 subjects.

CONCLUSIONS. Extremely few nonimmediate manifestations associated with cephalosporin therapy are actually hypersensitivity reactions, whereas most immediate reactions to cephalosporins are IgE-mediated. Cephalosporin skin testing is a useful tool for evaluating such reactions. *Pediatrics* 2008;122:521–527

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Key Words

cephalosporins, challenges, hypersensitivity reactions, intradermal tests, maculopapular rash, patch tests

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CEPHALOSPORINS MAY CAUSE several kinds of hypersensitivity reactions,¹ which are classifiable as immediate or nonimmediate according to the time interval between drug administration and reaction onset.² Immediate reactions occur within the first hour after the last drug administration and are manifested clinically by urticaria and/or angioedema, anaphylactic shock, rhinitis, and bronchospasm. Nonimmediate reactions occur >1 hour after the last drug administration. The main nonimmediate reactions are maculopapular or morbilliform rashes and delayed-appearing urticaria/angioedema.³ Rashes associated with cephalosporins are usually minor and non-life-threatening.^{4,5} Nevertheless, they may cause discomfort, parental anxiety, and visits to physicians, who often choose alternative antibiotics. This approach may impair good therapeutic outcomes and contribute to the problem of antibiotic-resistant strains.⁴ Therefore, it is important to evaluate children with these rashes.

In the present study, specific diagnostic protocols with standard techniques (skin tests, patch tests, serum specific IgE assays, and challenges) were applied to children with hypersensitivity reactions to cephalosporins, in an attempt to clarify the pathogenic mechanism involved. Specifically, according to the diagnostic protocols for evaluating

TABLE 1 Demographic Characteristics of the 148 Children Evaluated

	All Children (n = 148)	Children With Immediate Reactions (n = 43)	Children With Nonimmediate Reactions (n = 105)
Age, mean $\pm$ SD, y	6.87 $\pm$ 3.12	7.67 $\pm$ 3.25	6.55 $\pm$ 3
Girls, n (%)	71 (48)	24 (16.2)	47 (31.7)
Time since last cephalosporin reaction, median (range; interquartile range), mo ^a	8 (1–44; 3–16.5)	4 (1–44; 4–10)	10 (1–120; 4–9)
Family history of allergic diseases, n (%)	71 (48)	21 (14.2)	50 (33.8)
Personal history of allergic diseases, n (%)	38 (25.7)	10 (6.7)	28 (18.9)

^a Time between the last adverse reaction and the allergologic examination.

subjects with hypersensitivity reactions to β -lactams devised by the European Network for Drug Allergy, the European Academy of Allergology and Clinical Immunology interest group on drug hypersensitivity,^{6,7} children with immediate manifestations underwent immediate-reading skin tests, serum specific IgE assays, and, in cases of negative results, challenges, whereas subjects with nonimmediate manifestations were assessed with both patch tests and delayed-reading (ie, after 48 hours and even later) skin tests and, in cases of negative responses, with provocation tests.

METHODS

Study Group

We studied all children from 2 to 14 years of age with histories of hypersensitivity reactions to cephalosporins who were seen in the allergy units of the Columbus Integrated Complex and Oasi Maria Santissima Institute between January 1999 and June 2007 (Table 1). We questioned the parents of all of the children to identify the suspect antibiotic, as well as to obtain information about any adverse reactions to other drugs, particularly antibiotics. Symptoms were classified on the basis of medical records or, failing that, according to parents' descriptions. Before the study, the parents received information about the possible risks of skin and challenge tests, and written informed consent was obtained from them. The protocol was approved by the institutional review board. The children underwent the following allergologic tests.

Prick and Intradermal Skin Tests

The skin testing was performed on 3 different days, as described previously.⁸ On the first day, prick and intradermal tests were conducted by using penicilloyl polylysine (Allergopharma, Reinbeck, Germany), minor determinant mixture (Allergopharma), and benzylpenicillin (Pharmacia, Milan, Italy). The final concentrations were 5×10^{-5} mmol/L, 2×10^{-2} mmol/L, and 10 000 IU/mL, respectively. Because Allergopharma ceased production of penicillin reagents, from July 2005 we used Diater (Madrid, Spain) reagents, that is, penicilloyl polylysine (final concentration: 1.07×10^{-2} mmol/L) and minor determinant mixture (benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid; final concentration: 1.5 mmol/L). Penicilloyl polylysine and minor determinant mixture are not commercially available

in the United States. Ampicillin and amoxicillin, at concentrations of 1 mg/mL and 20 mg/mL, after dilution in 0.9% NaCl, were used on the second day. Responsible cephalosporins (Table 2), at a concentration of 2 mg/mL in 0.9% NaCl, were used on the third day. All cephalosporins were diluted with 0.9% NaCl no more than 2 hours before administration. For injectable cephalosporins, we used the intravenous form under sterile conditions; for noninjectable ones, we prepared a solution as described previously.⁸

All of the aforementioned reagents were initially tested on volar forearm skin with the prick method, and reactions were considered positive when a wheal >3 mm in diameter, with surrounding erythema, was present 20 minutes later. When prick tests yielded negative results, 0.02 mL of the reagent solution was injected intradermally on volar forearm skin. Readings were made 20 minutes after injections. Results were considered positive when an increase of >3 mm in the wheal diameter, accompanied by erythema, was present.^{8,9} Positive control assays for prick and intradermal tests were performed with histamine (at 10 and 1 mg/mL, respectively). As a negative control sample for prick and intradermal tests, 0.9% NaCl was used. The concentration used for cephalosporins proved to be non-irritating for 40 healthy subjects, as described previously.¹⁰ Reading of late reactions to intradermal tests was performed after 48 and 72 hours; any infiltrated erythema with a diameter of >5 mm was considered a positive reaction.

Patch Tests

In the first evaluation, patch tests were performed with benzylpenicillin, ampicillin, amoxicillin (5% in petrolatum; FIRMA, Florence, Italy), and any other suspect cephalosporins or β -lactams (at a concentration of 200 mg/mL in 0.9% NaCl), in addition to prick and intradermal tests with penicillin reagents. All reagents were applied to uninvolved skin on the interscapular region of the patient's back, by using acrylate adhesive strips with small plates attached for test allergens (Curatest; Lohmann & Rauscher, Rengsdorf, Germany). Occlusion time was 48 hours. Readings were made, as recommended by Brockow et al,⁹ 15 minutes after removal of the strips and 24 hours later. Control patch tests in 30 healthy subjects who had previously tolerated ≥ 1 of these β -lactams were also performed.

TABLE 2 Responsible Drugs and Related Adverse Reactions

Suspected Drugs	n (%)									Total
	Immediate Reactions (n = 43)				Nonimmediate Reactions (n = 105)					
	AS	UR	UA	ER	UR	UA	ER	ED	MP	
Cephalosporins										
Cefaclor	16	7	2	0	31	5	7	4	11	83 (34.6)
Ceftriaxone	9	4	1	2	8	0	2	3	5	34 (14.2)
Cefixime	1	1	0	0	10	2	1	0	4	19 (7.9)
Cefuroxime	0	0	0	0	3	0	2	0	1	6 (2.5)
Ceftibuten	0	0	0	0	2	0	1	1	2	6 (2.5)
Ceftazidime	2	0	0	0	1	0	0	0	1	4 (1.6)
Cefotaxime	0	0	0	0	2	1	0	0	0	3 (1.2)
Cefatrizine	1	0	0	0	0	0	0	0	1	2 (0.9)
Cephalexin	1	0	0	0	1	0	0	0	0	2 (0.9)
Cefazolin	0	0	0	0	0	0	0	0	1	1 (0.4)
Cefotetan	0	0	0	0	0	0	0	0	1	1 (0.4)
Cefprozil	0	0	0	0	0	0	0	0	1	1 (0.4)
Cefonicid	0	0	0	0	0	0	0	0	1	1 (0.4)
Total cephalosporins	30	12	3	2	58	8	13	8	29	163 (67.9)
Penicillins										
Amoxicillin	0	0	0	0	4	3	4	0	4	15 (6.3)
Amoxicillin plus clavulanic acid	0	0	0	0	7	1	2	1	4	15 (6.3)
Ampicillin	0	0	0	0	2	0	0	0	0	2 (0.9)
Ampicillin plus sulbactam	0	0	0	0	0	0	0	0	1	1 (0.4)
Benzylpenicillin	0	0	0	0	0	0	0	1	0	1 (0.4)
Other drugs										
Macrolides	0	0	0	0	19	0	5	1	11	36 (15)
NSAIDs	0	0	0	0	1	1	0	2	0	4 (1.6)
Other antibiotics	0	0	0	0	2	0	0	0	0	3 (1.2)
Total reactions	30 (12.5)	12 (5)	3 (1.2)	2 (0.85)	94 (39.2)	13 (5.4)	24 (10)	13 (5.4)	49 (20.45)	240 (100)

AS indicates anaphylactic shock; UR, urticaria; UA, urticaria and angioedema; ER, erythema; ED, edema; MP, maculopapular rash; NSAIDs, nonsteroidal antiinflammatory drugs.

Detection of Serum Specific IgE

Blood samples were collected when patients were evaluated, and serum samples were stored at -20°C until assayed. Assays for serum specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor (CAP-fluorescent enzyme immunoassays) were performed according to the manufacturer's instructions, with UniCAP (Phadia, Uppsala, Sweden), for all 43 children with immediate reactions. A positive result (ie, detectable specific IgE antibodies) was defined as a value of ≥ 0.35 kU/L.

Challenges

Challenges with responsible cephalosporins (noninjectable administered orally and injectable administered intramuscularly) were performed for subjects who displayed negative results in allergologic tests. For children with immediate reactions, we administered an initial dose of one 100th of the therapeutic dose (from 150 mg up to 1 g, depending on the child's weight). In cases with negative results, 1 hour later we administered a dose of one tenth of the therapeutic dose; if the results were again negative, then after another hour we administered a full dose. For children with nonimmediate manifestations, the interval between doses was 1 week, as described previously.^{7,11} In cases of positive responses to drugs in the form of syrups or suspensions, we performed a challenge with the same drug in the form of capsules or tablets. Each patient was carefully monitored

during test dosing, and complete equipment for cardiopulmonary resuscitation was immediately available.

Retesting

Children who had experienced immediate reactions >6 months before the allergologic evaluation and who displayed negative results in allergologic tests, including challenges, were given therapeutic doses of cephalosporins for 1 week and then reevaluated 4 weeks later.

Statistical Analysis

Data were prospectively collected and analyzed by using Statistica 6.0 for Windows (StatSoft, Tulsa, OK).

RESULTS

We examined a total of 148 children (71 girls and 77 boys), ranging in age from 2 to 14 years, with histories of hypersensitivity reactions to cephalosporins. Our evaluation was performed 8 months (range: 1–144 months) after the most recent cephalosporin adverse reaction. Both family and personal histories of allergic diseases were more frequent among children with nonimmediate reactions (Table 1). One hundred five children had experienced nonimmediate reactions and 43 immediate ones. Cefaclor and ceftriaxone were the cephalosporins most frequently responsible for both nonimmediate and immediate reactions. Of the 105 children with a total of 116 nonimmediate manifestations associated with cepha-

TABLE 3 Clinical Data and Allergologic Test Results for the 35 Children With a Diagnosis of IgE-Mediated Hypersensitivity to Cephalosporins

Patient	Gender	Age, y	Drug Involved	Type of Reaction	Test Results										
					Immunoassays (kU/L)					Skin Tests					
					PG	PV	AMy	AXy	Cefaclor	PPL	MDM	BP	AM	AX	Culprit
1	Male	10	Cefaclor	UA, UR	—	—	—	—	0.42	—	—	—	—	—	+
2	Male	13	Cephalexin	AS	—	—	—	—	—	—	—	—	—	—	+
3	Male	14	Ceftriaxone	AS	—	—	—	—	—	—	—	—	—	—	+
4	Female	10	Cefaclor	AS, AS	—	—	—	—	—	—	—	—	—	—	+
5	Male	4	Ceftriaxone	UR	—	—	—	—	—	—	—	—	—	—	+
6	Female	3	Cefaclor	UR	—	—	—	—	—	+	+	+	—	—	+
7	Female	12	Ceftriaxone	AS	—	—	—	—	—	—	—	—	—	—	+
8	Female	9	Ceftriaxone	AS	—	—	—	—	—	—	—	—	—	—	+
9	Female	5	Ceftriaxone	AS	—	—	—	—	—	—	—	—	—	—	+
10	Male	7	Cefaclor	AS	—	0.63	—	—	13.4	—	—	—	—	—	+
11	Female	12	Cefaclor	AS, UA, UR	—	—	—	—	—	—	—	—	+	+	+
12	Female	10	Cefaclor	AS	—	—	—	—	—	—	—	—	—	—	+
13	Male	4	Cefaclor	AS	1.02	3.31	—	—	—	—	—	—	—	—	+
14	Male	6	Ceftriaxone	UR	—	—	—	0.36	—	—	—	—	—	—	+
15	Female	10	Cefatrizine	AS	—	—	—	—	—	—	—	—	—	—	+
16	Female	7	Cefaclor	AS	—	—	—	—	—	—	—	—	+	—	+
17	Female	8	Ceftazidime	AS	—	—	—	—	—	+	+	—	—	+	+
18	Female	3	Cefaclor	AS	—	—	—	—	—	—	—	—	—	—	+
19	Female	3	Ceftriaxone	AS	—	—	—	—	—	—	—	—	—	—	+
20	Female	7	Cefaclor	AS	—	—	—	—	—	—	—	—	+	+	+
21	Male	4	Cefaclor	AS	—	—	0.64	0.42	—	—	—	—	—	—	+
22	Male	13	Cefaclor	UR	—	—	—	—	—	+	+	—	—	—	—
23	Female	7	Ceftriaxone	AS	—	—	—	—	—	—	—	—	—	—	+
24	Female	3	Cefaclor	UR	—	—	—	—	—	—	—	+	—	—	+
25	Male	4	Ceftriaxone	UR	—	—	0.35	—	—	—	—	—	—	—	+
26	Female	6	Ceftriaxone	AS	—	—	—	—	—	—	—	—	—	—	+
27	Female	13	Cefaclor	AS	—	—	—	—	—	—	—	+	+	+	+
28	Male	6	Cefaclor	AS	—	—	—	—	—	—	—	—	—	—	+
29	Male	5	Cefaclor	AS	—	—	—	—	—	—	—	—	—	—	+
30	Male	9	Ceftriaxone	UA	—	—	—	—	—	—	—	—	—	—	+
31	Male	4	Cefixime	UR	—	—	—	—	—	+	—	—	—	—	—
32	Male	8	Ceftriaxone	AS	—	—	—	—	—	—	—	—	—	—	+
33	Male	11	Cefaclor	AS	—	—	—	—	—	—	—	—	—	—	+
34	Female	10	Cefaclor	AS	—	—	—	—	1.17	—	—	—	—	—	+
35 ^a	Male	3	Ceftriaxone	UR	—	—	—	—	—	—	+	+	+	+	—

AS indicates anaphylactic shock; UR, urticaria; UA, urticaria and angioedema; PG, penicilloyl G; PV, penicilloyl V; AMy, ampicilloyl; AXy, amoxicilloyl; PPL, penicilloyl polylysine; MDM, minor determinant mixture; BP, benzylpenicillin; AM, ampicillin; AX, amoxicillin.

^a All reactions were immediate except for patient 35, who suffered a nonimmediate urticarial eruption associated with ceftriaxone and other nonimmediate urticarial eruptions associated with roxithromycin and netilmicin treatments.

alosporin therapies, 50 had reacted to a single cephalosporin, 4 to >1 cephalosporin, and the remaining 51 to cephalosporins and other drugs on separate occasions; among such other drugs, penicillins and macrolides were most frequently involved (Table 2). All of the 43 children with immediate manifestations had reacted to a single cephalosporin, experiencing a total of 47 episodes, because 3 of the children had experienced >1 reaction to cefaclor (Tables 2 and 3). The main nonimmediate manifestations associated with cephalosporins were urticarial eruptions (58 episodes) and maculopapular rashes (29 episodes), whereas the most frequent immediate reactions to cephalosporins were anaphylactic shock (30 episodes) and urticaria (12 episodes) (Table 2).

None of the nonimmediate reactors presented positive responses to patch tests and/or delayed-reading skin tests; only 1 subject displayed immediate positive responses to penicillin skin-test reagents (Table 3, child

35). Among the 104 patients with negative results, 8 refused challenges (Table 4) and 96 accepted them. One patient tolerated ceftriaxone but did not undergo challenges with cefaclor and ceftazidime (Table 4, child 12). One patient, a 4-year-old girl who had experienced an urticarial eruption during cefaclor therapy, reacted to the cefaclor suspension and tolerated the challenge with a cefaclor capsule; the remaining 94 children tolerated a total of 105 challenges with suspected cephalosporins. Forty-three of these 94 subjects also tolerated a total of 65 challenges with other suspected drugs, such as penicillins (28 challenges) and macrolides (31 challenges) (Table 5).

In the first allergologic evaluation, 33 (76.7%) of the 43 children with immediate reactions displayed skin-test positivity, 25 to the responsible cephalosporins, 6 to both penicillin reagents and the responsible cephalosporins, and 2 only to penicillin reagents; 7 of those 33 children

TABLE 4 Clinical Data for the 12 Children Who Refused or Did Not Complete the Challenge Tests

Patient	Gender	Age, y	Time Interval, mo	Drug Involved	Type of Reaction	Time of Onset
1	Male	9	48	Ceftriaxone	AS	Immediate
2	Female	8	9	Cefaclor	AS	Immediate
3	Male	11	11	Cefaclor	UR	Immediate
4	Male	7	72	Ceftazidime, ceftriaxone, erythromycin, azithromycin	MP, MP, MP, MP	Nonimmediate
5	Male	2	7	Cefaclor, AX	UA, UA	Nonimmediate
6	Female	6	12	Cefixime, ceftriaxone, erythromycin	UR, UR, UR	Nonimmediate
7	Female	7	24	Cefaclor, AX, AX+clav	UA, UA, UA	Nonimmediate
8	Female	6	10	Cefaclor, AX+clav	UR, UR	Nonimmediate
9	Female	6	1	Cefaclor, AX+clav, clarithromycin	UR, UR, UR	Nonimmediate
10	Male	3	2	Cefaclor, AX+clav	UA, MP	Nonimmediate
11	Male	4	1	Ceftriaxone	UR	Nonimmediate
12	Male	11	5	Ceftriaxone, cefaclor, ceftazidime	ED, UR, UR	Nonimmediate

AX indicates amoxicillin; AX+clav, amoxicillin plus clavulanic acid; AS, anaphylactic shock; UR, urticaria; UA, urticaria and angioedema; ED, edema; MP, maculopapular rash.

TABLE 5 Cephalosporins and Other Drugs Tested in the 177 Negative Challenges Performed for 103 Children

Suspected Drug	n (%)		
	Children With Immediate Reactions (n = 7)	Children With Nonimmediate Reactions (n = 96)	Total
Cephalosporins			
Cefaclor	1	53	54 (30.5)
Ceftriaxone	3	14	17 (9.6)
Cefixime	1	16	17 (9.6)
Ceftibuten	0	6	6 (3.35)
Cefuroxime	0	6	6 (3.35)
Cefotaxime	0	3	3 (1.7)
Ceftazidime	2	1	3 (1.7)
Cefatrizine	0	1	1 (0.6)
Cephalexin	0	1	1 (0.6)
Cefazolin	0	1	1 (0.6)
Cefotetan	0	1	1 (0.6)
Cefprozil	0	1	1 (0.6)
Cefonicid	0	1	1 (0.6)
Total cephalosporins	7	105	112 (63.4)
Penicillins			
Amoxicillin	0	13	13 (7.3)
Amoxicillin plus clavulanic acid	0	11	11 (6.2)
Ampicillin	0	2	2 (1.1)
Ampicillin plus sulbactam	0	1	1 (0.6)
Benzylpenicillin	0	1	1 (0.6)
Other drugs			
Macrolides	0	31	31 (17.5)
NSAIDs	0	4	4 (2.2)
Other antibiotics	0	2	2 (1.1)
Total	7 (4)	170 (96)	177 (100)

NSAIDs indicates nonsteroidal antiinflammatory drugs.

also demonstrated positive results in serum specific IgE assays (Table 3). Of the 10 patients with negative results, 3 refused challenges (Table 4) and 7 underwent them; for 4 of the latter subjects, challenges were followed by therapeutic courses and reevaluations. All challenges and therapeutic courses were tolerated; in the reevaluation, 1 girl, who had experienced anaphylactic shock in response to ceftazidime 14 months before the first allergologic examination, presented positive skin-test results

for both the responsible cephalosporin and penicillin reagents (Table 3, child 17).

Overall, IgE-mediated hypersensitivity was diagnosed for 34 (79%) of 43 subjects with immediate reactions and 1 (0.9%) of 105 subjects with nonimmediate manifestations. We did not identify any responsible additives, excipients, or coloring agents for the girl who had reacted to the challenge with cefaclor suspension, because her parents refused challenges with those substances.

DISCUSSION

In the present study, 33 (76.7%) of the 43 children with immediate reactions displayed positive results in the first allergologic evaluation, whereas only 1 (0.9%) of the 105 children who had experienced nonimmediate manifestations did. As far as immediate reactions are concerned, skin testing with the suspected cephalosporins at a concentration of 2 mg/mL proved to be a useful tool for evaluating the 43 children with such reactions. In effect, 31 (72.1%) of them displayed positive responses to skin tests with cephalosporins in the first evaluation. Therefore, the sensitivity of cephalosporin skin testing in the present study was similar to that (69.7%; 53 of 76 patients) found in the first evaluation in a previous study of ours with adults.⁸ With regard to the literature data concerning children, Atanasković-Marković et al¹² assessed 1170 children with immediate reactions to penicillins and/or cephalosporins; 682 (58.3%) of them displayed immediate responses to skin tests or challenges. Of those 682 children, 27.9% demonstrated positive skin-test results for cefaclor, 24.9% for cephalexin, 0.9% for ceftriaxone, and 0.3% for cefotaxime; the rates of positive responses to challenges with cefaclor, cephalexin, and ceftriaxone were 1.3%, 0.9%, and 0.1%, respectively. In a study by Pichichero and Pichichero,¹³ 13 (50%) of the 26 children with hypersensitivity reactions to cephalosporins displayed immediate positive responses to cephalosporin skin tests or challenges, including 2 subjects who had suffered a maculopapular rash. Ponvert et al¹⁴ evaluated 325 children with histories of hypersensitivity reactions to β -lactams, including cephalosporins; only 4 (1.2%) of them displayed immediate positive skin-test responses to cephalosporins.

The rate of resensitization, diagnosed on the basis of conversion to skin-test positivity in patients retested ~1 month after negative challenge results followed by full therapeutic courses, observed in the present study (25%; 1 of 4 children) was lower than that found in the aforementioned study of adults (83.3%; 5 of 6 subjects).⁸ This resensitization phenomenon has been described in other studies,^{13,15–18} with frequency rates ranging from 0.9%¹⁵ to 16.6%.¹⁶ Moreover, negative skin-test results were observed for both children and adults with IgE-mediated hypersensitivity to penicillins who were retested after ≥ 1 year^{19,20}; some subjects tolerated penicillin again.¹⁹ Therefore, for children with immediate reactions to cephalosporins who present negative skin-test results when evaluated >6 months after their last reaction, the pathogenic mechanism can be clarified by performing challenges with suspect cephalosporins and, in cases of negative responses, by administering a full therapeutic course and retesting 3 to 4 weeks later.

Fourteen (32.5%) of the 43 subjects with immediate reactions displayed skin-test and/or AP fluorescent enzyme immunoassay positivity to penicillin reagents; most of them had reacted to cefaclor (Table 3). Cross-reactivity to penicillins can be hypothesized, considering that cefaclor and ampicillin have the same side chain. However, coexisting sensitivities to cephalosporins may occur in penicillin-allergic subjects.²¹ Also, some children could have been sensitized earlier to a particular penicillin, which would not automatically imply cross-reactivity to the culprit cephalosporin. The serum specific IgE assay proved to be of little use, because positive cases also displayed immediate responses to skin tests. With regard to cefaclor, this assay was positive for only 3 (16.6%) of the 18 children who had suffered immediate reactions to this cephalosporin; these 3 subjects also demonstrated positive skin-test results for cefaclor.

With regard to nonimmediate reactions, both patch tests and delayed-reading intradermal tests were negative for the 105 children with such manifestations associated with cephalosporins, including the 31 subjects who had experienced maculopapular rashes, which were associated with cephalosporins (22 subjects), cephalosporins and aminopenicillins (7 subjects), and aminopenicillins (2 subjects). However, positive responses to both of these tests allowed us to diagnose a cell-mediated pathogenic mechanism for 4 (9.5%) of 42 children who had experienced maculopapular rashes associated with aminopenicillins and had been evaluated in a previous study of ours.¹¹ In the aforementioned study by Ponvert et al,¹⁴ 10 (3%) of the 325 children demonstrated positive skin-test results in early (ie, after 8 hours) or delayed (ie, after 48–72 hours) assessments. In addition, cell-mediated hypersensitivity was diagnosed on the basis of positive responses to patch tests with the responsible cephalosporins for 2 children, who had experienced a maculopapular rash and erythema multiforme, respectively, and had been assessed in separate studies.^{22,23}

In the present study, all 96 subjects with nonimmediate reactions and negative results in allergologic tests who underwent challenges tolerated them (Table 5). Therefore, the negative predictive value of both patch

tests and delayed-reading intradermal tests was very high, as in previous studies that challenged subjects with histories of nonimmediate reactions to cephalosporins and negative results in delayed-reading intradermal tests and/or patch tests.^{14,24} Specifically, in a study by Lamintausta and Kortekangas-Savolainen,²⁴ only 1 of the 75 patients with cutaneous eruptions associated with cephalosporins (cefadroxil or cephalexin) and negative results in allergologic tests reacted to challenges with the suspect cephalosporin (cefadroxil). Although the negative predictive value of delayed-reading intradermal tests and patch tests seems to be high, negative results in such tests do not completely rule out immunologic mechanisms. Although additional comprehensive studies are needed, negative results in these tests with an appropriate panel seem to indicate that most of the nonimmediate cutaneous eruptions associated with cephalosporins are not hypersensitivity reactions but rather manifestations of the underlying infectious diseases, particularly those affecting the respiratory and urinary tracts,^{25,26} for which the antibiotics were prescribed. Some nonimmediate reactions, including urticarial and maculopapular ones, may result from interactions between viruses and antibiotics.²⁷ In fact, in many hypersensitivity reactions to drugs, stimulation of the immune system by viruses such as Epstein-Barr virus or HIV leads to reactions in >50% of infected individuals.²⁸

CONCLUSIONS

In evaluating children with suspected hypersensitivity reactions to cephalosporins, it is useful to distinguish between nonimmediate and immediate manifestations. Most of the latter are IgE-mediated, and cephalosporin skin testing is a sensitive tool for evaluating such reactions. However, it is difficult to attribute a nonimmediate cutaneous eruption to either infection or drug intake only on the basis of the clinical history. Therefore, although delayed hypersensitivity to cephalosporins in children seems to be rare, it is useful to assess subjects with nonimmediate reactions by performing delayed-reading skin tests and, in cases of negative results, challenges.

Finally, our diagnostic evaluation allowed us to clarify the nature of the manifestations experienced by 136 (91.9%) of the 148 children studied. Immediate hypersensitivity was diagnosed for 35 subjects (23.6%); for 101 subjects (68.2%), negative challenge results ruled out a diagnosis of cephalosporin hypersensitivity at the time of evaluation. Definitive diagnoses could not be provided for the remaining 12 subjects (8.1%), who either did not undergo challenges or did not complete them (Table 4).

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