

Letter to the Editor

Diagnosing nonimmediate reactions to cephalosporins

To the Editor:

Like penicillins, cephalosporins can cause nonimmediate reactions (ie, occurring >1 hour and within 7 days after the last drug administration).¹ The main nonimmediate reactions are maculopapular or morbilliform rashes and delayed-appearing urticaria/angioedema.² There are studies^{3,4} suggesting that either delayed-reading intradermal tests or patch tests, or both can be an effective way of diagnosing a delayed hypersensitivity in subjects who have experienced nonimmediate reactions to cephalosporins. However, few studies have been performed in samples larger than 100 subjects with such reactions.^{4,5} In a study by Lamintausta and Kortekangas-Savolainen,⁴ cephalosporins elicited positive patch test reactions in 12 (4.1%) of 290 patients with cutaneous adverse reactions to these β -lactams. In a study of ours,⁵ none of the 105 children with nonimmediate reactions to cephalosporins displayed positive responses to either patch tests or delayed-reading intradermal tests.

In the present study, according to the diagnostic protocol devised by the European Network for Drug Allergy,⁶ subjects with histories of nonimmediate reactions to cephalosporins were assessed by using both patch tests and delayed-reading (ie, after ≥ 48 hours) skin tests and, in case of negative responses, by provocation tests in an attempt to clarify the pathogenic mechanism involved.

We studied prospectively all patients seen in the allergy units of Complesso Integrato Columbus and Oasi Maria Santissima between January 2004 and December 2010 reporting nonimmediate reactions during cephalosporin therapy. We carefully questioned patients to identify the suspect antibiotic and to obtain an accurate description of symptoms. The protocol was approved by the respective institutional review boards.

After obtaining the informed consent of the patients (or the parents of those <18 years of age), on the first day, we performed skin prick and intradermal tests using penicilloyl-polylysine, minor determinant mixture, and benzylpenicillin, as previously described.⁵ In the second evaluation 2 days later, we used ampicillin and amoxicillin at concentrations of 1 and 20 mg/mL, as well as the suspect cephalosporins at a concentration of 2 mg/mL and any other suspect penicillins (Table I) at concentrations of 1 and 20 mg/mL.

The reagent preparation, skin tests, and immediate (ie, at 20 minutes) readings were performed as previously described.^{5,7,8} Positive controls for skin prick and intradermal tests were performed with histamine (at 10 and 1 mg/mL, respectively). As a negative control for skin prick and intradermal tests, normal saline was used.

After the evaluation of patient 13 of this series (patient 1 of Table II), we used the suspect aminocephalosporins (cephalexin, cefaclor, and cefatrizine) at concentrations of 2 and 20 mg/mL. The latter concentration proved to be nonirritant in 30 control subjects, 20 of whom had tolerated at least 1 of these aminocephalosporins.

Readings of late reactions to intradermal tests were done after 48 and 72 hours; any infiltrated erythema with a diameter larger than 5 mm was considered a positive reaction.

In addition to skin prick and intradermal tests with penicillin reagents, in the first evaluation we administered patch tests with benzylpenicillin, ampicillin, and amoxicillin, as well as with suspect cephalosporins and any other suspect penicillins (5% in petrolatum), as previously described.⁵ Occlusion time was 48 hours. Readings were made, as recommended by Brockow et al,⁸ 15 minutes after removal of the strips and 24 hours later.

Subjects with negative results in all of the above tests or who displayed a doubtful response underwent challenges with the suspect cephalosporin concerned: cephalexin (1 g), cefaclor (500 mg), cefixime (400 mg), ceftibuten (400 mg), cefatrizine (500 mg), cefprozil (500 mg), cefpodoxime (200 mg), and cefuroxime axetil (500 mg) administered orally or ceftriaxone, ceftazidime, cefotaxime, cefamandole, cefazolin, cefonicid, and cefepime (1 g) administered intramuscularly. We administered an initial dose of one hundredth of the therapeutic one. In patients with negative results, 1 week later, we administered a dose of one tenth and, if the result was again negative, a full dose after another week, as previously described.⁶ After the first 40 challenges, to shorten this challenge work-up, we administered an initial dose of one tenth of the therapeutic one and, if the result was negative, a full dose 1 hour later.

Each patient was carefully monitored during challenges until 4 hours after the administration of the dose; complete equipment for cardiopulmonary resuscitation was immediately available.

Data were prospectively collected and analyzed with the Statistica 6.0 software for Windows (StatSoft, Tulsa, Okla). Categorical data were given as numbers of cases and percentages, and they were compared by using a χ^2 test. The differences between means were evaluated by using the Student *t* test for unpaired data. A *P* value of .05 or less indicates statistical significance.

We examined a total of 105 subjects (75 female and 30 male subjects) ranging in age from 14 to 84 years (mean age, 39 ± 16.9 years) with histories of nonimmediate reactions to cephalosporins. Our work-up was performed with intervals ranging from 1 to 312 months (median, 11 months) after the most recent adverse reaction.

Patients had a total of 144 reactive episodes (143 nonimmediate episodes and 1 episode of anaphylactic shock); 75 had reacted to a single cephalosporin, 2 had distinct reactions to different cephalosporins in separate episodes, and the remaining 28 had reactions to cephalosporins and other drugs on separate occasions. Penicillins, macrolides, and nonsteroidal anti-inflammatory drugs were the primary compounds involved other than cephalosporins (Table I).

The suspect cephalosporins and the clinical manifestations described by the subjects are listed in Table I. These manifestations lasted for a mean of 3.76 days (SD, 4.4 days; range, 1-30 days) after the cephalosporin therapy was discontinued.

Three subjects showed both positive patch test and positive delayed intradermal test results to the culprit cephalosporins (Table II, patients 2, 5, and 7), whereas 2 (Table II, patients 3 and 4) presented only a delayed positive intradermal test result to these cephalosporins.

One patient (Table II, patient 1) experienced a maculopapular rash with diffuse angioedema during cephalexin therapy, had negative patch test results, and displayed a doubtful response

TABLE I. Suspect drugs and related adverse reactions in the 105 subjects

Suspect drugs	Adverse reactions						Total, no. (%)
	MP	UR	ER	ED	UA	Others	
Cephalosporins							
Ceftriaxone	11	9	10	2	0	0	32 (22.2)
Cephalexin	7	3	3	1	2	0	16 (11.1)
Ceftazidime	5	2	2	2	2	0	13 (9)
Cefixime	5	2	2	1	1	0	11 (7.6)
Cefaclor	4	1	1	1	0	0	7 (4.9)
Cefotaxime	2	2	0	2	0	0	6 (4.2)
Cefazolin	0	2	0	0	2	0	4 (2.8)
Cefuroxime axetil	2	1	0	0	1	0	4 (2.8)
Cefonicid	0	1	0	1	0	1	3 (2.1)
Ceftibuten	1	1	0	1	0	0	3 (2.1)
Cefamandole	1	1	0	0	0	0	2 (1.4)
Cefprozil	1	0	1	0	0	0	2 (1.4)
Cefpodoxime	0	1	1	0	0	0	2 (1.4)
Cefatrizine	0	1	0	1	0	0	2 (1.4)
Cefepime	0	0	0	1	0	0	1 (0.7)
Cefuroxime	0	1	0	0	0	0	1 (0.7)
Cefodizime	0	0	0	0	0	1	1 (0.7)
Total cephalosporins, no. (%)	39	28	20	13	8	2	110 (76.4)
Penicillins							
Amoxicillin + clavulanic acid	4	1	0	0	1	0	6 (4.2)
Amoxicillin	4	1	0	0	0	0	5 (3.5)
Piperacillin	0	1	0	0	0	1*	2 (1.4)
Piperacillin + tazobactam	0	0	1	0	0	0	1 (0.7)
Bacampicillin	1	0	0	0	0	0	1 (0.7)
Ampicillin	0	1	0	0	0	0	1 (0.7)
Unknown penicillin	0	0	1	0	0	0	1 (0.7)
Other drugs							
Macrolides	3	2	2	0	1	0	8 (5.5)
NSAIDs	0	2	2	0	1	0	5 (3.5)
Quinolones	1	0	0	0	2	0	3 (2.1)
Betamethasone	0	1	0	0	0	0	1 (0.7)
Total reactions, no. (%)	52 (36.1)	37 (25.7)	26 (18)	13 (9)	13 (9)	3 (2.1)	144 (100)

ED, Edema; ER, erythema; MP, maculopapular rash; UA, urticaria and angioedema; UR, urticaria.

*Anaphylactic shock.

TABLE II. Clinical data and allergologic test results of the 7 patients with cephalosporin allergy

Patient no.	Sex	Age (y)	Responsible drugs	Type of reaction	Time interval* (mo)	Delayed-reading skin tests						Patch tests				Challenges		
						PPL	MDM	BP	AM	AX	Culprit	BP	AM	AX	Culprit			
1	F	45	Cephalexin	MP	132	—	—	—	+	+	+/-†	—	+	+	—	+‡		
2	F	31	Cephalexin	MP	36	—	—	+	+	+	+	+	+	+	+	NP		
3	F	59	Ceftriaxone	MP	4	—	—	—	—	—	+	—	—	—	—	NP		
4	F	53	Cefaclor	ED	4	—	—	—	—	—	+	—	—	—	—	NP		
5	F	84	Ceftriaxone	MP	2	—	—	—	—	—	+	—	—	—	+	NP		
6	F	52	Cefodizime	LR	84	+	(i)	—	—	+	+	+	(i)	—	+	+	—	NP
7	F	26	Unknown penicillin	ER	14	—	—	—	—	—	+	—	—	—	+	NP		
			Ceftriaxone	MP														

AM, Ampicillin; AX, amoxicillin; BP, benzylpenicillin; ED, edema; (i), immediate reading; LR, local reaction; MDM, minor determinant mixture; MP, maculopapular rash; NP, not performed; PPL, penicilloyl-polylysine.

*Time elapsed between the last cephalosporin reaction and current allergologic testing.

†Cephalexin was tested at 2 mg/mL; after this case, cephalexin, cefaclor, and cefatrizine were tested at 2 and 20 mg/mL.

‡Maculopapular rash 48 hours after 10 mg of cephalexin.

(an infiltrated erythema with a diameter of 3 mm) to the delayed-reading intradermal test with cephalexin at 2 mg/mL; she agreed to undergo the cephalexin challenge and reacted to one hundredth of the therapeutic dose, experiencing a mild maculopapular rash 48 hours later.

Another patient (Table II, patient 6) had a diffuse erythema during therapy with a semisynthetic penicillin, as well as a local reaction (infiltrated erythema with a diameter of 11 cm lasting 4 days) 3 hours after the second intramuscular injection of cefodizime. She presented immediate responses to intradermal tests

with penicilloyl-polylysine and cefodizime, as well as patch test and delayed-reading intradermal test result positivity to ampicillin and amoxicillin.

One patient, who had experienced a nonimmediate urticarial eruption during ceftriaxone therapy and anaphylactic shock after intramuscular piperacillin, had a positive response to the immediate-reading intradermal test to piperacillin only. He underwent a ceftriaxone challenge and tolerated it.

Of the 98 subjects with negative results in cephalosporin allergologic tests, 86 accepted challenges (91 in all) with the suspect cephalosporins and tolerated them. Among the latter subjects, 26 underwent a total of 30 additional challenges with suspect drugs other than cephalosporins, with negative results.

Taking into account only the manifestations associated with cephalosporin therapy, the mean time of their resolution was longer in the group of 6 patients (Table II, patients 1-5 and 7) with a delayed hypersensitivity (13.6 ± 7.3 days; range, 7-21 days) than in the remaining 99 subjects (3.31 ± 4.3 days; range, 1-30 days). This difference is statistically significant ($t = -5.43$, $P < .001$).

Overall, on the basis of the results of testing, 1 patient displayed both an IgE-mediated hypersensitivity to cefodizime and a delayed hypersensitivity to aminopenicillins; a delayed hypersensitivity was confirmed in 6 of the 37 subjects who had experienced maculopapular rashes associated with cephalosporin therapy, and none of the 68 subjects with other manifestations had positive test results. However, a definitive diagnosis could not be provided for 12 (11.4%) subjects who refused challenges.

The classification of drug hypersensitivity reactions as immediate and nonimmediate based on a time interval of 1 hour between the last drug administration and clinical manifestations has some limits. In effect, some IgE-mediated reactions, such as that experienced by patient 6 of Table II, occur more than 1 hour after the last drug administration. For this reason, the European Network for Drug Allergy diagnostic algorithm concerning non-immediate reactions to β -lactams⁶ includes immediate-reading (at 20 minutes) skin tests in addition to patch tests and delayed-reading skin tests.

In the present study most delayed skin manifestations in temporal correlation with cephalosporin treatments did not show a sensitization on intradermal skin tests nor could they be reproduced in a provocation test. Thus allergy alone does not seem to be a sufficient explanation for them.

It is interesting to note that the mean time for resolution of generalized skin reactions was significantly longer in the patients with sensitization than in the patients without sensitization (13.6 vs 3.31 days). However, it is difficult to attribute nonimmediate manifestations associated with cephalosporin therapy to either such therapy or infection only on the basis of the clinical history, even though, according to the observation of the present study, a duration of 1 week or more suggests a delayed hypersensitivity. Patch tests and delayed-reading intradermal tests are useful tools in evaluating nonimmediate reactions to β -lactams, particularly maculopapular rashes.^{1,6} In accordance with the literature data,⁶ in the present study delayed-reading intradermal tests revealed more sensitization to the involved drug than patch tests (5/105 vs 3/105).

What we observed in patient 1 of Table II suggests that the concentration of 20 mg/mL used for intradermal tests with aminocephalosporins might reduce the number of subjects with false-negative results at the concentration of 2 mg/mL. In effect,

patients 2 and 4 of Table II presented responses to intradermal tests at 20 mg/mL larger than those produced by testing at 2 mg/mL.

It is interesting to note that 2 (Table II, subjects 1 and 2) of the 3 subjects with a delayed hypersensitivity to aminocephalosporins displayed a cross-reactivity with aminopenicillins (ampicillin and amoxicillin), which share an amino group in the side chains with aminocephalosporins.⁹

In the present study the rate of positive responses to delayed-reading intradermal tests is low (4.7% [5/105 subjects]). However, it is noteworthy that excluding the patient with a doubtful response to intradermal testing with cephalixin (Table II, patient 1), the remaining 86 subjects with negative results in delayed-reading intradermal tests who underwent challenges with the suspect cephalosporins tolerated them. This suggests a good sensitivity of skin tests. Nevertheless, our challenge protocol with the administration of a single full therapeutic dose might be insufficient to elicit clinical manifestations in patients with only a mild sensitization.

Although more extensive and detailed studies would be useful, negative results on allergologic tests using an appropriate panel appear to be a fairly reliable indicator that the cutaneous eruptions associated with cephalosporin therapy are not allergic reactions but might be manifestations of infectious agents (eg, EBV and HIV) or result from interaction between viruses and antibiotics, as in infectious mononucleosis.¹⁰

In conclusion, intradermal tests are useful tools in identifying the cephalosporins responsible for nonimmediate reactions. However, considering the results of the present study, patch testing is not indicated in subjects with mild nonimmediate reactions to cephalosporins, such as maculopapular and urticarial rashes.

Antonino Romano, MD^{a,b}
Francesco Gaeta, MD, PhD^a
Rocco Luigi Valluzzi, MD^a
Cristiano Caruso, MD^a
Cristiana Alonzi, MD, PhD^a
Marinella Viola, MD^a
Philippe Jean Bousquet, MD^{c,d}

From ^aAllergy Unit, Complesso Integrato Columbus, Rome, Italy; ^bIRCCS Oasi Maria S.S., Troina, Italy; ^cDépartement de Biostatistique, Epidémiologie, Recherche Clinique, Santé Publique et Information Médicale, Hôpital Carémieu, BESPI, GHU Caremau, Nîmes, France; and ^dExploration des Allergies, Hôpital Arnaud de Villeneuve, Montpellier. E-mail: antoninoromano@h-columbus.it.

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