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Cross-reactivity and Tolerability of Cephalosporins in Patients With Cell-Mediated Allergy to Penicillins

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Abstract

Background and objective: β-Lactams are the most commonly used antibiotics but they can cause hypersensitivity reactions. We sought to estimate cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins.
Methods: We studied 97 patients with a clinical history of nonimmediate reactions to a penicillin and a positive patch test result to at least 1 of the penicillins tested. All patients also underwent patch testing with several cephalosporins. Patients with a negative patch test to a cephalosporin underwent test dosing in order to assess tolerability.
Results: We recorded 129 reactions. The most commonly involved drugs were aminopenicillins, and the most widely reported symptoms were delayed urticaria and maculopapular exanthema. Seventeen patients had positive patch test results for cephalosporins, mostly for cephalexin (n=10), cefaclor (n=9), and cefuroxime axetil (n=5). All the patients—except 4 who experienced an exanthema after the challenge test with cephalexin—tolerated a therapeutic dose of the cephalosporin tested without any adverse effects.
Conclusions: Our data show that cross-reactivity between penicillins and cephalosporins may be as high as 10.9% for first-generation cephalosporins and 1.1% for third-generation cephalosporins, possibly due to the involvement of similar side chains. Patch tests are a useful diagnostic tool to assess cross-reactivity, but a graded challenge is mandatory because a negative patch test does not always mean tolerability.

Key words: Cell-mediated hypersensitivity. Cephalosporins. Cross-reactivity. Penicillins.

Resumen

Introducción y objetivo: Los antibióticos betalactámicos son los más comúnmente utilizados y pueden ser responsables del desarrollo de reacciones de hipersensibilidad. Este estudio pretende estimar la reactividad cruzada y la tolerancia a las cefalosporinas en pacientes con alergia mediada por células a penicilinas.
Métodos: Estudiamos 97 pacientes con historia clínica de reacciones no inmediatas a penicilina y que habían tenido una prueba de parche positiva al menos frente a una de las penicilinas testadas. También se realizó parche frente a alguna cefalosporina en todos ellos. Los pacientes con negatividad en esta prueba se sometieron a la prueba de tolerancia.
Resultados: Se recopilaron 129 reacciones, la mayoría de los medicamentos implicados fueron aminopenicilinas, siendo los síntomas más frecuentes la urticaria de aparición tardía y el exantema máculo-papular. Diecisiete pacientes arrojaron resultados positivos en la prueba del parche a cefalosporinas, cefalexina (10 casos), ceflacor (9) y acetil-cefuroxima (5). Todos los pacientes excepto 4 (los cuales tuvieron un eccema tras la provocación con cefalexina), toleraron la dosis terapéutica de la cefalosporina probada sin ningún efecto dañino.
Conclusiones: Según nuestros resultados, la reactividad cruzada entre penicilinas y cefalosporinas es de 10,9% para las cefalosporinas de primera generación y de 1,1% para las de tercera generación. Esto puede ser debido a las cadenas similares implicadas. La prueba del parche es una herramienta diagnóstica útil para evaluar la reactividad cruzada, pero necesita una provocación gradual, dado que una prueba del parche negativa no implica tolerancia.

Palabras clave: Hipersensibilidad mediada por células. Cefalosporinas. Reactividad cruzada. Penicilinas.

Introduction

Penicillins and cephalosporins are 2 classes of β-lactam antimicrobial agents. They are the most widely used antibiotics for treating common infections and are also used as first-line prophylaxis for many types of surgical procedures. However, they frequently cause both IgE-mediated and cell-mediated hypersensitivity reactions.

Penicillins and cephalosporins both have a 4-member β-lactam ring (BLR), but the 5-member thiazolidine (THIAZ) ring of penicillins is replaced by the 6-member dihydrothiazine (DHT) ring in the cephalosporin nucleus. Side chains, which may be bound to the BLR or the THIAZ or DHT rings, are other important antigenic determinants that may be responsible for cross-reactivity.

The estimated risk of developing hypersensitivity reactions to cephalosporins ranges from 1% to 3% and is higher in patients with documented penicillin allergy. Approximately 1% to 10% of patients with IgE-mediated allergy to penicillins may also develop an immediate hypersensitivity reaction to cephalosporins. Recent data suggest that this cross-reactivity may be much higher (17.38%), while other papers have reported a rate of 10.9% for cephalothin and cefamandole, and of 6% for first-generation cephalosporins [1-3].

These conflicting reports have led to a certain confusion about the administration of cephalosporins to patients allergic to penicillin, and this in turn could cause under- or overestimation of the risk involved. Because of the fear of cross-reactivity, the most common therapeutic approach in penicillin-allergic patients is to select a class of antibiotics that does not contain the BLR, such as quinolones or macrolides. Such a strategy, however, may have major drawbacks, including reduced effectiveness, increased antimicrobial resistance, and higher costs [4].

Several studies have analyzed cross-reactivity and tolerability between penicillins and cephalosporins in patients with IgE-mediated allergy to penicillins, but less attention has been paid to patients with cell-mediated allergy to penicillins [5-7]. Cell-mediated allergy to penicillins is a serious medical problem that has become increasingly relevant in recent decades [8]. While cell-mediated allergy to drugs cannot cause anaphylaxis, it can lead to drug discontinuation and cause severe systemic reactions (drug rush with eosinophilia and systemic symptoms) and cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis).

The main aim of our study was to retrospectively assess cross-reactivity between penicillins and cephalosporins in a large group of patients with well-documented cell-mediated, delayed-type allergy to penicillins. Moreover, patients with negative cephalosporin skin test results were challenged to ascertain tolerability.

Materials and Methods

Patient Selection

From our database we selected all patients with a clinical history of nonimmediate reactions to any penicillin between 2002 and 2011. Nonimmediate reactions encompass all reactions that take more than 1 hour to appear after the last drug administration. To be included in our study, patients had to have a positive patch test to at least 1 penicillin (penicillin G, penicillin V, ampicillin, amoxicillin, bacampicillin, piperacillin, mezlocillin, and ticarcillin). We evaluated sensitization to cephalosporins using skin tests with cephalexin (a first-generation cephalosporin) and cefaclor (a second-generation cephalosporin), which have the same α-amino side chain as aminopenicillins (ampicillin, amoxicillin, and bacampicillin), as well as with cefuroxime axetil (a second-generation molecule) and ceftriaxone, ceftibuten, and cefotaxime (third-generation molecules), which share the same aminothiazole side chain on the 4-atom β-lactam ring, and cefixime. Some patients with negative skin test results were administered some of these cephalosporins following consent. The exclusion criteria were pregnancy; cardiovascular, renal, or respiratory disease; and concomitant IgE-mediated hypersensitivity to any β-lactam compound.

Written informed consent was obtained from all participants or their parents in the case of patients younger than 18 years of age.

Skin Tests

Immediate-type skin tests (prick and intradermal) were performed with penicilloyl-polylysine (PPL), minor determinant mixture (MDM), penicillin G, penicillin V, amoxicillin, bacampicillin, piperacillin, ticarcillin, mezlocillin, imipenem-cilastatin, aztreonam and cephalosporins (cephalexin, cefaclor, cefuroxime axetil, ceftriaxone, ceftibuten, cefixime, and cefotaxime) according to the indications of the European Academy of Allergy and Clinical Immunology [9,10].

In 2004, Allergopharma (Allergopen) stopped production of PPL and MDM reagents (containing 0.5 mg of benzyl-penicillin and 0.6 mg of benzylpenicilloate) and we therefore switched to PPL and MDM reagents (containing 0.5 mg of sodium benzyl-penicillin, 0.5 mg of benzyl-penicilloic acid, and 0.5 mg of benzylpenicilloate) produced by Diater Laboratorios in 2004. The agreement between the skin test results with the reagents from the 2 companies was very high: 100% for MDM and 97.4% for PPL [11].

Immediate-type skin tests were carried out with preparations for parenteral use first by prick testing and then, in the case of a negative result, by intradermal testing. For prick tests with drugs not commercially available for parenteral use, the tablets were ground in a mortar and the powder was dissolved in saline. The concentrations of drugs used for immediate-type skin and patch tests are listed in Table 1. Reactions were considered positive when the diameter was at least 3 mm greater than the negative control in the case of prick tests and at least 5 mm greater in the case of intradermal tests. Histamine at a concentration of 10 mg/mL and saline were used as positive and negative controls, respectively. Immediate-type skin tests were read after 20 minutes and also after 48 hours to check for delayed reactions. A positive delayed reaction was considered to include induration of the skin and erythema with a diameter of over 5 mm [9,12].

Table 1. Concentrations of β-Lactams for Parenteral Use for Intradermal Tests

Drug	Concentration
Penicillin G	100-10 000 U/mL
Ampicillin	2-20 mg/mL
Amoxicillin	2-20 mg/mL
Ticarcillin	2-20 mg/mL
Piperacillin	2-20 mg/mL
Mezlocillin	2-20 mg/mL
Imipenem-cilastatin	0.1-1 mg/mL
Aztreonam	0.2-2 mg/mL
Injectable cephalosporins	0.2-2 mg/mL

Patch Tests

Patch tests were carried out using the same drugs as those used for the prick and intradermal tests. All drugs were mixed in petrolatum at 25% w/w for ampicillin and amoxicillin and at 20% w/w for the other drugs. The patches were applied to the interscapular region and evaluated after 72 hours. Patch results were scored according to the indications of the European Network on Drug Allergy: doubtful reaction = faint erythema; weak positive reaction (+) = erythema, induration, and discrete papules; strong positive reaction (++) = erythema, induration, papules, and vesicles; and extremely positive reaction (+++) = intense erythema, induration, and coalescing vesicles. Petrolatum was used as a negative control [9,12].

In Vitro Tests

Specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor (UniCAP, Pharmacia) was also tested for on evaluation. A value of 0.35 kU/L or greater was considered positive. Blood samples were obtained at evaluation and sera were stored at –20°C until assayed.

Cephalosporin, Aztreonam, and Imipenem-Cilastatin Test Dosing

Challenges with cefuroxime axetil (500 mg orally), cefixime (400 mg orally), ceftibuten (400 mg orally), cephalexin (500 mg orally), ceftriaxone (1 g intramuscularly), aztreonam (1 g intramuscularly), and imipenem-cilastatin (500 mg intramuscularly) were performed only in patients with negative delayed intradermal and patch tests. An initial dose of one-hundredth of the therapeutic dose was administered. In the case of a negative result, one-tenth of the therapeutic dose was administered after 1 hour, and if the result was still negative, a full dose was administered an hour later. Each patient was carefully monitored during the test dosing and was seen again after 24 and 48 hours because of the possibility of a delayed reaction.

Aztreonam and imipenem-cilastatin test dosing are described in detail elsewhere [13,14].

Patients with a positive patch test result for a cephalosporin were not challenged with another molecule sharing the same side chain because of the higher risk of cross-reaction.

Results

We studied 97 patients ranging in age from 15 to 75 years, with histories of nonimmediate reactions to penicillins. We performed the allergy testing after an interval ranging from 1 to 360 months from the time of the most recent reaction. The patients had experienced a total of 129 reactions to penicillins. The offending drugs were mainly aminopenicillins and the most reported symptoms were delayed urticaria and maculopapular exanthemas (with or without angioedema) (Tables 2 and 3).

All the participants had a positive delayed reading and/or patch test to at least 1 penicillin reagent (Table 3). Of the 97 patients, 17 had a positive patch test to at least 1 of the cephalosporins tested: 10 had positive results with cephalexin, 9 with cefaclor, 5 with cefuroxime axetil, and the remaining 6 had different patterns of patch test positivity. Immediate-type skin tests (skin prick and intradermal tests) and specific IgE to the tested molecules were negative in all individuals.

Table 2. Clinical Data of Patients (n=97)

Variable	Value
Mean (SD) age (25-75 percentile), y	44.7 (16.6) (30.75-59)
Men, No. (%)	26 (26.8%)
Median time since last penicillin reaction (range) (25-75 percentile), mo	85.8 (1-360) (9.5-144)
Reactions, No.[a]	129
Culprit β-lactams, No. (%)	
Amoxicillin	50 (38.7)[b]
Ampicillin	35 (27.1)[c]
Bacampicillin	25 (19.4)
Penicillin G	11 (8.5)
Unknown β penicillin	7 (5.4)
Topical penicillin	1 (0.8)
Manifestations, No.	
Delayed urticaria	32 (24.8)
Maculopapular exanthema	26 (20.1)
Maculopapular exanthema + angioedema	25 (19.4)
Delayed appearing urticaria + angioedema	17 (13.2)
Generalized erythema	16 (12.4)
Angioedema	9 (7)
Generalized itching	1 (0.8)
Contact dermatitis	1 (0.8)
Stevens-Johnson syndrome	1 (0.8)
Erythema multiforme	1 (0.8)

[a]Some patients had more than 1 reaction.
[b]Of these reactions, 18 were also with clavulanic acid.
[c]Of these reactions, 2 were also with cloxacillin and 1 was also with sulbactam.

Table 3. Allergy Test Results[a]

Patient	Culprit Drugs	Positive Patch Tests	Positive Delayed Intradermal Tests	Negative Challenge Tests	Positive Challenge Tests
1	Ax + Cla	PG, PV, Ax		I, Cef, Az, Ctx, Cfu	
2	U	PG, PV, Am, Ax, Ti	PG, Am, Ax, Ti	Az, Cfu, Cef	
3	Am, B	PG, PV, Am, Ax, B	PG, Am, Ax	I, Az, Cef, Cft	
4	Ax, Ax	Am, Ax, B	Am, Ax	Az, I, Cfu, Cef, Cfl	
5	Ax	Am, Ax, B	Am, Ax	Az, I, Ctx, Cft, Cef	
6	Am	PG, PV, Am, Ax, B, Pi, M	PG, Am, Ax, Pi, M	Az, I, Cfu, Cef	
7	Ax + Cla	PG, PV, Am, Ax, B	PG, Am, Ax	Cfu, Cef	
8	Ax + Cla	Am, Ax, B	Am, Ax	I, Az, Cef, Cft	
9	Ax	Am, Ax, B	Am, Ax	I, Cfu, Cef, Ctx	
10	Ax	Am, Ax, B	Am, Ax	Az, I, Cef	
11	Am	Am, Ax, B, **Cfc**	Am, Ax	Az, I, Cfu, Cef, Cft	
12	Ax + Clav	Am, Ax, B, Pi, Ti	Am, Ax, Pi, Ti	I, Az	
13	PG	PG, PV, Am, Ax, B, Pi	PG, Am, Ax, Pi	I, Az, Cfu, Ctx, Cft, Cef	
14	Am, B	PG, PV, Am, Ax, B, Pi	PG, Am, Ax, Pi	I, Az, Cfl, Cft, Ctx	
15	PG, Am	Am, Ax, B	Am, Ax	I, Az, Cfl, Cfu, Cft	
16	B	Am, Ax, B	Am, Ax	I, Az, Cfl, Cfu, Cft	
17	PG	PG, PV, Am, Ax, B	PG, Am, Ax	I, Az, Cfl, Cfu, Cft	
18	Ax, PG	PG, PV, Am, Ax, B, Pi, Ti, M, I, **Cfu, Clc, Cfl**	PG, Am, Ax, Pi, Ti, M	Az, Cft	
19	Am + Clo, Am + Cl	PG, PV, Am, Ax, B, Pi, I, **Clc, Cfl**	PG, Am, Ax, Pi	Az, Cft, Cfu	
20	PG	PG, PV, Am, Ax, B, Ti	PG, Am, Ax, Ti	Az, I, Cfl, Cfu, Cft	
21	U	PV		N.d.	
22	PG, PG	PG, PV, B, Pi, M, Ti	PG, Pi, M, Ti	Az, I, Cft, Cfu	
23	Ax, Ax	PG, PV, Am, Ax, B	PG, Am, Ax	Az, I, Cfl, Cfu, Cft, Ctx	
24	B	PG, PV, Am, Ax, B, Pi	PG, Am, Ax, Pi	Az, I, Cfl, Cft, Cef	
25	Ax	PG, PV, Am, Ax, B, M, Ti, I	PG, Am, Ax, M, Ti	Az, Cfu, Cft, Ctx	
26	Ax	Am, Ax, B	Am, Ax	Az, I, Cfu, Cft	
27	B	PG, PV, Am, Ax, B	PG, Am, Ax	Az, I, Cfl, Cfu, Ctx, Cft	
28	Ax	PV, Am, Ax, B, Pi, Ti	Am, Ax, Pi, Ti	Cft, I	
29	Ax	PG, PV, Am, Ax, B, Pi, M, Ti	PG, Am, Ax, Pi, M, Ti	Az, I, Cft	
30	PG	PG, PV		Az, I, Cft	
31	Am, Ax	PG, PV, Am, Ax, B, Pi, M, Ti , I, Cfl	PG, Am, Ax, Pi, M, Ti	Az, Cft, Ctx	
32	Am, Ax + Cla	Am, Ax, B	Am, Ax	Az, I, Cfl, Cft, Ctx	
33	Am	Am, Ax, B, Cfl	Am, Ax	Cft	
34	Am	PG, PV, Am, Ax, B, Ti	PG, Am, Ax, Ti	Az, I, Cfl, Cfu, Cef, Cft	
35	Am	Am, Ax, B	Am, Ax	Az, I, Cfl, Cfu, Cft, Ctx	
36	Ax, B	PV, Am, Ax, B, Ti	Am, Ax, Ti	Az, I, Cfu, Cft	Cfl
37	U	PG, PV, Am, Ax, B, Pi, M	PG, Am, Ax, Pi, M	Az, I, Cfl, Cfu, Cft, Ctx	
38	B, Ax	Am, Ax, B	Am, Ax	Az, I, Cfl, Cft, Ctx	
39	Ax + Cla	PV, Am, Ax, B, Ti	Am, Ax, Ti	Az, I, Cfl, Cfu, Cft	
40	Am	PG, Am, Ax, B	PG, Am, Ax	Az, I, Cft	
41	B	Am, Ax, B	Am, Ax	Az, I, Cfl	
42	Am	Am, Ax, B, **Cfc**	Am, Ax	Az, I, Cft	Cfl
43	Ax	Am, Ax, B	Am, Ax	Az, I, Cfl, Cft	
44	B	Am, Ax, B	Am, Ax	Az, I, Cfu, Cft, Ctx, Cfl	
45	B	Am, Ax, B	Am, Ax	Az, I, Cfu, Cft	Cfl
46	Am	Am, Ax, B	Am, Ax	Cfl, Cfu, Cft	
47	B	Am, Ax, B	Am, Ax	Az, I, Cfl, Cft, Ctx	
48	B	PG, PV, Am, Ax, B, **Cfl, Cfc**	PG, Am, Ax	Az, Cft, Ctx, Cfu	
49	PG	PG, PV, Am, Ax, B, M	PG, Am, Ax, M	Az, I, Cfl, Cfu, Cef, Ctx	

Patient	Culprit Drugs	Positive Patch Tests	Positive Delayed Intradermal Tests	Negative Challenge Tests	Positive Challenge Tests
50	B	Am, Ax, B	Am, Ax	Az, I, Cfl, Cft, Ctx	
51	Am, B	Am, Ax, B	Am, Ax	Az, I, Cfl, Cef, Cfu, Ctx	
52	B	Am, Ax, B	Am, Ax	Az, I, Cfl, Cef, Ctx	
53	PG	PG, PV, Am, Ax, B, **Cef, Cfu**	PG, Am, Ax	Az, I	
54	Ax	Am, Ax, B	Am, Ax	Az, I, Cfl, Cfu, Cef	
55	B	Am, Ax, B	Am, Ax	Az, I, Cfl, Cfu, Cft	
56	Am	Am, Ax, B, Pi	Am, Ax, Pi	Az, I, Cfl, Cef, Cft	
57	TP	PG, PV, Ti	PG	Az, Cfl, Cfu, Cft, Ctx	
58	Am	PG, Am, Ax, B, M	PG, Am, Ax	Az, I, Cfl, Cfu, Cef	
59	Am, Am, Ax + Cla	PG, PV, Am, Ax, B, Pi, Ti, M	PG, Am, Ax, Pi, Ti, M	Az, I, Cfl, Cfu, Cef,Ctx	
60	Ax, Ax	Am, Ax, B	Am, Ax	Az,I, Cfl, Cfu, Cef	
61	U, U	PG, PV, Am, Ax, B, Ti	PG, Am, Ax, Ti	I	
62	Ax + Cla	Am, Ax, B	Am, Ax	Az, I, Cef, Ctx	
63	B	PG, PV, Am, Ax, B	PG, Am, Ax	I, Cfu, Cef, Ctx	
64	Am, Ax	Am, Ax, B	Am, Ax	Az, I, Cfl, Cef, Cfu	
65	Ax + Cla	Am, Ax, B	Am, Ax	I, Cef	
66	B, Ax	Am, Ax, B	Am, Ax	Az, I, Cef	
67	Am	PG, PV, Am, Ax, B, Ti, **Cfu, Cfc**	PG, Am, Ax, Ti	Az, I, Cft, Ctx	
68	Ax + Cla	Am, Ax, B	Am, Ax	Az, I	
69	Am	PG, PV, Am, Ax, B, Ti, **Cfu, Cfc**	PG, Am, Ax, Ti	I, Cef	
70	Am	Am, Ax, B, **Cfl, Cfu**	Am, Ax	Az,, Cef	
71	Ax, B	Am, Ax, B	Am, Ax	Cef	
72	Ax+ Cla, Am + Sul	PG, PV, Am, Ax, B, Pi, Ti	PG, Am, Ax, Pi, Ti	Az, Cfu, Cef	
73	Ax + Cla	Am, Ax, B	Am, Ax	Cfu, Cef	
74	Ax, Am	Am, Ax, B, Pi	Am, Ax, Pi	Cfu, Cef, Ctx	
75	B, Am	PG, Am, Ax, B M, Ti	PG, Am, Ax, M, Ti	Az, Cfu	
76	Am, Am	PV, Am, Ax, B, Pi, Ti	Am, Ax, Pi, Ti	Az, Cfu, Cef	
77	Ax	PG, PV		Az, Cef	
78	B	PV, Am, Ax, B	Am, Ax	Az, Cfu, Cef, Ctx	
79	Ax	PG, PV, Am, Ax, B	PG, Am, Ax	Cfu, Cef	
80	Am, Am, Ax	Am, Ax, B	Am, Ax	Az, Cef	
81	Am, Am	Am, Ax, B	Am, Ax	Az, Cfu, Cef, Ctx	Cfl
82	Ax + Cla	Am, Ax, B, Pi, **Cfl**	Am, Ax, Pi	Az, Cef	
83	B, Ax	Am, Ax, B, Pi, **Cfl**	Am, Ax, Pi	I, Cef	
84	B, Am	PG, PV, Am, Ax, B, Ti	PG, Am, Ax, Ti	N.d.	
85	Ax	Am, Ax, B	Am, Ax	Az, Cfu, Cef	
86	Ax	Am, Ax, B	Am, Ax	I, Cfu, Cef	
87	B, B, Ax + Cla	Am, Ax, B	Am, Ax	Az, I, Cef	
88	Ax	Am, Ax, B	Am, Ax	Az, Cfl, Cef	
89	Ax + Cla	Am, Ax, B	Am, Ax	Az, Cfu, Cef	
90	PG	PG, B		Cfl, Cft	
91	Ax + Cla	Am, Ax, B, **Cfc**	Am, Ax	Cef	
92	Ax + Cla	Am, Ax, B, **Cfl**	Am, Ax	Cfu, Cef, Ctx	
93	U	Am, Ax, B	Am, Ax	Cfu, Cef	
94	B	PV, Am, Ax, B, Pi, **Cfu**	Am, Ax, Pi	N.d.	
95	U	PG, PV, Am, Ax, B, Pi, **Cfc**	PG, Am, Ax, Pi	Az, Cfu, Cef, Ctx	
96	Ax, Ax + Cla	Am, Ax, B, Ti	Am, Ax, Ti	Az, Cfu, Cef	
97	Ax	Am, Ax, B	Am, Ax	Az, Cfu, Cef, Ctx	

Abbreviations: Ax, amoxicillin; Az, aztreonam; B, bacampicillin; Cef, cefixime; Cfc, cefaclor; Cfl, cephalexin; Cft, ceftibuten; Cfu, axetil-cefuroxime; Cl, cloxacillin; Cla, clavulanic acid; Ctx, ceftriaxone; I, imipenem; M, mezlocillin; PG, penicillin G; PV, penicillin V; Pi, piperacillin; TP, topic penicillin; Sul, sulbactam; Ti, ticarcillin; U, unknown.
[a]Cephalosporins are indicated in bold.

We performed 42 challenge tests with cephalexin, 56 with cefuroxime axetil, 50 with cefixime, 42 with ceftibuten, 32 with ceftriaxone, 76 with aztreonam, and 62 with imipenem-cilastatin. Challenge tests were negative in all patients except 4, who experienced a maculopapular exanthema the day after the challenge with cephalexin, showing cross-reactivity (Table 3).

Discussion

The risk of an allergic reaction to cephalosporins in patients with a history of penicillin allergy may be up to 8 times higher than that in individuals with no history of penicillin allergy [4].

Romano et al [8] studied 128 patients with positive immediate-type skin tests to at least 1 penicillin reagent and found that 14 patients (10.9%) also had positive skin tests to at least 1 cephalosporin, specifically cephalothin and cefamandole [2]. Our data confirm that more recently developed molecules have lower cross-reactivity with penicillins because they share different side chains; aminopenicillins were the most frequently involved molecules in delayed reactions.

The increased risk of allergic reactions to cephalosporins in patients allergic to penicillins was recently confirmed. In fact Park et al [3] recommend caution or avoidance in administering cephalosporins to penicillin-allergic patients, while Liu et al [1] reported cross-reactivity between cephalosporins and penicillins, and stated that third-generation cephalosporins may also cause cross-allergic reactions with penicillins in penicillin-allergic patients. On the basis of our data, we found that aminocephalosporins have the highest risk of cross-reactivity with penicillins in delayed reactions, while cefixime and ceftriaxone usually lack cross-reactivity with penicillins and are well tolerated.

Other authors found no cross-reactivity between penicillins and the cephalosporins cefuroxime, cephazoline, and ceftriaxone in penicillin-allergic patients. However, they all agreed that allergy testing with cephalosporins is mandatory before performing a graded challenge [15,16]. Considering the uncertainty that still surrounds this topic, administration of cephalosporins to penicillin-allergic patients is often deferred because of the fear of cross-reactivity.

All existing studies have been performed in patients with IgE-mediated allergy to penicillins and in patients with a clinical history of penicillin hypersensitivity; no large studies in patients with well-established cell-mediated allergy to penicillin are available. The aims of our study were, first, to assess cross-reactivity between penicillins and cephalosporins and, second, to assess tolerability of certain cephalosporins only in patients with delayed-type allergy to penicillins.

A cross-reactivity rate of 31.25% has been observed for cephalexin in patients with cell-mediated allergy to ampicillin, but the series consisted of just 16 patients; tolerability of cephalexin was then assessed in 5 patients with negative patch tests by means of a graded challenge, with no adverse effects observed [17]. The authors concluded that a delayed reaction to ampicillin was not necessarily a contraindication to the use of cephalexin. However, 4 of our patients had a delayed reaction after the challenge with cephalexin, despite a negative patch test. Other authors found no cross-reactivity between penicillins, cefpodoxime, and cefixime in 71 patients with delayed allergy to penicillins [18].

In our series, patients 33, 42, 70, 91, and 92 had selective aminopenicillin allergy and showed cross-reactivity with cephalexin and/or cefaclor, which share the same α-amino side chain. Patients 42, 45 and 81 had a positive challenge test with cephalexin (despite a negative patch test) and they all had positive patch tests with aminopenicillins. Our results are similar to previous observations that cross-reactivity is higher for amino-cephalosporins (cephalexin, cefaclor) and lower for other second- and third-generation cephalosporins (cefuroxime axetil, ceftriaxone, cefixime) [2,19]. This may be explained by the fact that many first-generation cephalosporins and cefaclor share the same side chain as aminopenicillins and this side chain has been shown to be the most important antigenic determinant in delayed reactions [20].

In the other cases we did not find any specific cross-reactivity patterns. In such cases, it may be hypothesized that the β-lactam ring (new antigenic determinant), which is common to both penicillins and cephalosporins, may be involved. However, we should also consider that more complex antigenic structures may be the result of molecule processing and protein folding during antigen processing via the endogenous pathway.

Recent reviews have reported that cross-reactivity between penicillins and second- and third-generation cephalosporins is negligible and that administration of cephalosporins with different side chains can be considered a safe therapeutic approach [21,22]. This may be because the side chain (especially the α-amino group) is the most frequently involved antigenic determinant and is not usually present in recently developed cephalosporins.

In our study, negative patch test results seem to predict tolerability, except in the case of cephalexin. We are not able to explain this. All the patients had a clinical history of a nonimmediate reaction to an aminopenicillin and just 1 had a positive patch test to cefaclor, which shares the same side chain. The lack of injectable reagents for cephalexin may be responsible for this phenomenon. All of the patients tolerated other cephalosporins. We therefore recommend caution when using an aminocephalosporin in patients with positive patch tests to aminopenicillins and/or a clinical history of aminopenicillin hypersensitivity.

Even though it was not the main aim of our study, we found that aztreonam did not display cross-reactivity with penicillins and that the cross-reactivity of imipenem was very low.

On the basis of our results, when cephalosporin treatment is required in patients with cell-mediated allergy to penicillins, we recommend performing allergy tests to assess cross-reactivity followed by a graded challenge to establish tolerability. This approach is time-consuming, and unfeasible if a cephalosporin is urgently needed. In such a case, an alternative non-β-lactam antibiotic should be administered. If a cephalosporin is the only therapeutic option, a graded challenge with a cephalosporin with low cross-reactivity (with a different side chain) such as ceftriaxone, axetil-cefuroxime, or cefixime may be performed as a first-line option. Desensitization for delayed-type allergy to drugs is not unanimously accepted among scientists.

Cell-mediated reactions usually do not put the life of patients at risk, but they may cause discomfort and lead to

the interruption of treatment. For this reason, even if cross-reactivity between penicillins and cephalosporins is low, we recommend performing allergy testing before using a cephalosporin in patients with cell-mediated allergy to penicillins.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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