

DELAYED ALLERGY TO AMINOPENICILLINS: CLINICAL AND IMMUNOLOGICAL FINDINGS

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Aminopenicillins are the most used β -lactam antibiotics. Morbilliform or maculopapular rashes are rather frequent during therapy with aminopenicillins. The pathogenesis of these reactions is often due to a cell-mediated allergy. The aim of this work is to characterize patients with cell-mediated allergy to aminopenicillins and to identify alternative β -lactam drugs that can be safely administered to these patients. We studied 27 subjects affected by cell-mediated allergy to aminopenicillins. The diagnosis was made on the basis of positivity of patch tests with aminopenicillins. These patients then underwent an allergological evaluation (skin and patch tests, oral and/or intramuscular challenge tests) with a wide spectrum of β -lactam antibiotics. Our work highlights the following main characteristics of cell-mediated allergy to aminopenicillins: time elapsing between drug administration and onset of symptoms of about 2 days; the maculopapular rash and delayed appearance of urticaria/angioedema were the most typical symptoms (82.8% of cases); a cross-reactivity with aminocephalosporins is usually absent, or it is limited to cephalexin (in our study, in fact, just 3 out of 20 patients challenged with cephalexin showed a positive oral challenge test); all the β -lactams, other than aminopenicillins, are well tolerated. Patch tests represent a specific diagnostic tool with a good predictive value of identifying alternative drugs that can be safely administered to patients with β -lactam allergy. Our patients could tolerate other β -lactam drugs after a complete allergological evaluation. On the basis of our study, cell-mediated allergy to aminopenicillins should be considered a well-defined nosologic entity.

β -lactams, that include penicillins, cephalosporins, carbapenems, monobactams and β -lactamase inhibitors, are the most used antimicrobial drugs in clinical practice. The drugs most used in the penicillin group are aminopenicillins (1) that encompass ampicillin, amoxicillin and ampicillin ester compounds (bacampicillin, pivampicillin, talampicillin, cyclacillin); they all have an α -amino side chain that is an aminobenzyl in ampicillin and an amino-*p*-hydroxy-benzyl in amoxicillin (this

explains the theoretical cross-reactivity between aminopenicillins and aminocephalosporins: cephalexin, cefaclor, cefadroxil, cefatrizine and cefradine that have the same side chain) (2-3). Their wide use in clinical practice is responsible for the high incidence of adverse reactions, such as morbilliform or maculopapular rashes (4-6).

According to Levine (7), hypersensitivity reactions to penicillins can be classified into: immediate, that occur within the first hour after

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drug administration; accelerated, that occur 1 to 72 hours after drug administration; delayed, that take more than 72 hours to appear. While immediate reactions are mainly IgE-mediated (anaphylactic shock, urticaria-angioedema, asthma), accelerated and delayed reactions, such as the morbilliform rash, are mainly cell-mediated (8). β -lactams are also responsible for other clinical manifestations, such as delayed-appearing urticaria/angioedema, exfoliative dermatitis and more severe bullous exanthems like the Stevens-Johnson syndrome and the toxic epidermal necrolysis.

Cell-mediated reactions have risen in importance during the last few years and are now more frequent than those IgE-mediated. In fact, in a previous work (9), our group found that a pathogenetic switch seems to be occurring from a type I to a type IV hypersensitivity mechanism within allergy to β -lactams; in 1987 the ratio between type I and IV was 1.14 while in 1997 it resulted as 0.86. Moreover, in agreement with data from literature, we also found that aminopenicillins are mainly associated with a cell-mediated hypersensitivity mechanism (9-11).

Three different antigenic epitopes within the penicilloyl group (the immunological structure of the penicillin molecule) can be put into evidence (12-13):

- 1) the new antigenic determinant (NAD), resulting from the opening of the β -lactam ring and conjugation of the amino group to endogenous proteins;
- 2) the thiazolidine ring (THIAZ);
- 3) the side chain (SC).

It was later shown that other antibodies could be detected with a not well-defined specificity directed towards a bridge structure stretching along the NAD and the SC, as well as antibodies directed towards not well-defined parts of the molecule (14).

The conjugation to endogenous proteins, the molecular structure of the SC (that is different between all β -lactams) and its dimension, and the exposition or the obstruction of single groups in the molecule affect the antigen presentation and antigen-antibody interaction responsible for the induction of a delayed-type response instead of an IgE-mediated one.

In our work we characterise, from a clinical and diagnostic point of view, patients with cell-mediated allergy to aminopenicillins to identify alternative β -lactam drugs that can be safely administered to these

patients.

MATERIALS AND METHODS.

From a population of 165 patients with allergy (63 with IgE-mediated allergy, 89 with cell-mediated allergy and 13 with mixed-type allergy) to β -lactams, we chose 27 (16.36%) subjects with cell-mediated allergy to aminopenicillins, demonstrated by: 1) positivity of patch tests to aminopenicillins; 2) negativity of patch tests with other β -lactams; 3) negativity of skin prick and intradermal tests with all β -lactams; 4) absence in serum of specific IgE to penicillin G, penicillin V, amoxicillin, ampicillin and cefaclor. As a control group we chose 20 patients who could tolerate aminopenicillins and other β -lactams and who did not undergo any challenge tests.

All subjects underwent a complete allergological evaluation consisting of immediate-type skin (prick and intradermal) and patch tests with penicilloyl-polylysine (PPL), Minor Determinant Mixture (MDM), penicillin G, penicillin V, amoxicillin, ampicillin, bacampicillin, ureido-penicillins, carboxy-penicillins, carbapenems, monobactams and 1st, 2nd and 3rd generation cephalosporins (Table I). Informed consent was obtained by all patients and the study was approved by our ethical board.

Immediate-type skin tests

Skin prick tests (SPT) were performed by pricking the skin percutaneously with a prick needle through an allergen solution. Intradermal tests (IT) were accomplished by injecting 0.02-0.05 ml of an allergen intradermally, raising a small bleb measuring 3 mm in diameter. Both SPT and IT were performed on the volar surface of the forearm (15).

For PPL, immediate-type skin tests were performed employing a commercial kit (Allergopen, Merck, Italy) containing 0.035 mg/mL, utilising undiluted and 1:10 solutions, while for MDM we used a commercial kit (Allergopen, Merck, Italy) containing 0.5 mg of benzil-penicillin and 0.6 mg of benzyl-penicilloate per mL, using 1:10 and 1:10,000 solutions. Immediate-type skin tests with other β -lactams were carried out with the preparation for parenteral route first by prick and, if negative, intradermally; for SPT of drugs unavailable on the market for parenteral use, the tablets were crushed in a mortar and the powder was dissolved in saline (15) (see Table I for concentrations).

Evaluation of immediate-type skin tests was assessed after 20 minutes, and again 48 hours later if any delayed reaction occurred. Histamine as positive control and saline as negative control were employed. Reactions at least 3 mm > than controls in diameter for prick tests and >5 mm for intradermal tests were considered positive. Delayed

reactions (after 48 hours) were considered positive if an infiltrated erythema with a diameter > 5 mm occurred.

Patch tests

Patch tests were performed with the same drugs as for immediate-type skin tests. All drugs were applied on the interscapular region of the patient's back by using acrylate adhesive strips with small plates (1 cm in diameter) attached for test allergens. We used 0.1 mL of undiluted commercial solutions for PPL and MDM, 5000 I.U. in vaseline for penicillin G, and 0.1 mL of the concentrations indicated in Table I for the other β -lactams.

Patch tests were evaluated 48 and 72 hours later, according to Wilkinson (16):

- 0: negative reaction;
- $\pm$: doubtful reaction;
- +: erythema, oedema, infiltration;
- ++: erythema, oedema, vesicles or papules;
- +++: spreading vesicles, ulcerative or bullous reactions.

All patch tests were prepared just before being applied.

In vitro tests

Specific IgE to penicillin G, penicillin V, ampicillin, amoxicillin and cefaclor and total IgE were also detected (UniCAP, Pharmacia, Uppsala, Sweden).

Immunochemical study

Cutaneous biopsies were then obtained by positive patch tests. They were taken by an 8-mm punch. They were snap-frozen in Tissue-Tek embedding solution (Miles Lab, Naperville, IL, U.S.A.) with liquid nitrogen and stored at -80°C . For immunochemical staining, specimens were cryostat-sectioned at $4\mu\text{m}$ intervals. These sections were thaw-mounted on polylysine hydrobromide-coated slides (Polyscience Inc, Warrington, PA, U.S.A.) and allowed to air-dry for 3 hours. All subsequent steps were performed at room temperature. Sections were fixed for 10 minutes at 100% acetone. Endogenous peroxidase activity was blocked by treating samples with chloroform for ten minutes. The slides were then rehydrated in 0.05 M TRIS-buffered saline (TBS), pH 7.6. Sections were then incubated for 30 minutes in normal serum, followed by an incubation of 1 hour with the following monoclonal antibodies: anti-CD3, anti-CD4, anti-CD8 and anti-CD20 (Dako, Glostrup, Denmark).

Isotype-matched controls were employed. Staining was achieved by the avidin-biotin peroxidase technique (ABC ELITE detection system; Vector, Burlingame, CA, U.S.A.). Hydrogen peroxide, normal goat blocking serum, biotinylated immunoglobulins, avidin-biotin complexes and 3-amino-9-ethyl-ethylcarbazole substrate solutions

were used according to the manufacturer. Sections were counterstained with toluidine blue 0.5% for two minutes and then dehydrated in isopropyl alcohol and mounted in Permount. Evaluation using light microscope followed.

Oral and intramuscular challenge tests

Oral (OCT) or intramuscular challenge tests (ICT) were carried out with β -lactams other than aminopenicillins in order to assess tolerance to alternative drugs that can be safely used by our patients. Increasing doses of the drug at 30-minute intervals were administered until the therapeutic dose was reached (Table I). Four subjects underwent oral provocation tests with aminopenicillins. Every challenge test was performed with a 7 day-interval from another.

Statistical analysis

The negative predictive value of the patch test was then calculated.

RESULTS

Patients

Twenty-two out of 27 allergic patients were female and 5 were male (ratio F/M = 4,4). All patients were aged from 14 to 72 years, with a predominance in the third and fourth decade (63%). A personal history of atopy was found in 2 subjects (7.4%), of urticaria in 4 (14.8%) and of adverse reactions to other drugs, except β -lactams, in 11 (40.7%). A familial history of atopy was found in 8 subjects (29.6%) and of adverse reactions to drugs other than β -lactams in just 1. Patients had a total of 35 reactive episodes. Amoxicillin was the culprit drug in 16 cases (45.7%), followed by ampicillin in 10 (28.6%) and by bacampicillin in 9 (25.7%). In 33 cases the drug had been administered orally and in 2 intramuscularly. The symptoms reported were mainly cutaneous: urticaria/angioedema in 13 cases (37.1%), maculopapular rash in 13 (37.1%), erythema in 4 (11.4%), urticaria and maculopapular rash in 3 (8.6%), erythema and fever in 1 (2.9%) and erythema and dyspnoea in 1 (2.9%). In 5 (14%) cases the patients were treated with antihistamines, in 11 (32.5%) with corticosteroids and in 4 (11%) with corticosteroids and antihistamines; in the remaining cases no therapy was needed.

Our work-up was performed from 1 month to 20 years after the most recent drug administration, with a mean of about 5 years. The time elapsing between

drug administration and onset of symptoms was of about 38.5 hours (standard deviation 45.92).

Immediate-type skin tests

In patients with delayed allergy to aminopenicillins, all immediate-type skin prick and intradermal tests resulted negative after 20 minutes. Immediate-type skin tests carried out with the other penicillins, carbapenems, monobactams and cephalosporins were all negative.

As regards the control group, skin tests were all negative.

Patch tests

Patch tests with aminopenicillins (ampicillin, bacampicillin and amoxicillin) were positive in all 27 patients; patient N. 11 also had a positive reaction to cephalixin; patch tests with other β -lactams were all negative (Table II). One patient presented a systemic reaction (slight erythema, itching of the throat, nasal and conjunctival pruritus) after 48 hours from the application of patch tests (therapy with oral antihistamines was needed). Patch tests were all negative in the control group.

In vitro tests

Specific IgE to penicillin G, penicillin V, ampicillin, amoxicillin and cefaclor were negative in all patients (<0.35 kU_A/L). Total IgE were within normal ranges in 22 cases out of 27 (normal value <200 kU_A/L; mean 140.36 ± 263.54 kU_A/L).

Immunochemical study

Just two patients underwent a cutaneous biopsy; the microscopical findings showed a lymphocytic infiltrate around superficial and deep vascular plexi associated with epidermal spongiosis and oedema of papillary dermis. Most cells within the infiltrate were CD3+ lymphocytes. There was a predominance of CD4+ cells as compared with CD8+ ones. Also some B lymphocytes were found (Fig. 1).

Challenge tests results

Oral or intramuscular challenge tests were performed in all our 27 allergic patients with the following drugs: penicillin G (11 ICT), penicillin V (18 OCT), piperacillin (13 ICT), mezlocillin (5 ICT), ticarcillin (4 ICT), imipenem (25 ICT),

aztreonam (23 ICT), cephalixin (20 OCT), cefaclor (12 OCT), cefradine (1 OCT), cefadroxil (7 OCT), cefatrizine (3 OCT), actoxyethyl-cefuroxime (10 OCT), cefuroxime (7 ICT), cefamandole (1 ICT), cefixime (9 OCT), ceftibuten (18 OCT), ceftriaxone (9 ICT), cefpodoxime (3 OCT) and cefepime (1 ICT); in total, 200 tolerance challenge tests were carried out (Table III).

All patients could tolerate the above-mentioned drugs except 3 patients who experienced a maculopapular rash after oral administration of cephalixin (which is a 1st generation cephalosporin belonging to the aminocephalosporin group). One of these patients had a positive patch test to cephalixin. Four patients underwent some oral provocation tests (OPT) with the responsible drugs: bacampicillin in 3 cases and ampicillin in 1 case; all OPT resulted positive.

Statistical analysis

Patch tests showed to have a negative predictive value of 98.5%.

DISCUSSION.

The objective of our study is to put in evidence the main clinical characteristics of patients with "delayed-type allergy to aminopenicillins", which is mediated by a IV-type (cell-mediated) hypersensitivity mechanism, and to assess the tolerance of a large number of β -lactam molecules in this group of patients (9). This nosologic entity is important since it represents 16.36% of all patients with allergy to β -lactams and 30.34% of all cases of delayed-type allergy to β -lactams. Our results highlight that delayed-type allergy to aminopenicillins is much more frequent in females than in males and in the 3rd and 4th decades; a personal history of atopy, of urticaria or of adverse drug reaction seems not to be important. Maculopapular rash and delayed-appearing urticaria are the most typical symptoms. The onset of symptoms is about 2 days after the beginning of the therapy and this is explained by the involvement of a cell-mediated mechanism.

The SC seems to play a very important role to cause a IV type allergic reaction rather than a I type one; in fact delayed type allergies to aminopenicillins are more frequent than IgE-mediated ones and the last ones are often associated to a contemporary

Table I. β -lactams used for *in vivo* tests.

Drugs	Skin tests concentrations	Patch test concentrations (in vaseline)	Tolerance challenges		
			Rout	D I (mg)*	D II (mg)*
Penicillin G	0.2-2000 IU/ml	5 %	Im	0.25-2.5-25 kU	250-250-500 kU
Penicillin V	1000.000 IU/ml	5 %	PO	0.25-2.5-25 kU	250-250-500 kU
Ampicillin	1 mg/ml	25 %	PO	5-10-15-20	50-100-150-200
Amoxicillin	1 mg/ml	25 %	PO	5-10-15-20	50-100-150-200
Bacampicillin	90 mg/ml	20%	PO	8-16-24-32	80-160-240-320
Piperacillin	5 mg/ml	20 %	Im	20-40-80	160-320-520
Mezlocillin	2.5 mg/ml	20 %	Im	20-40-80	160-320-520
Ticarcillin	6 mg/ml	20%	Im	20-40-80	120-360-720
Imipenem	2.5 mg/ml	20 %	Im	10-20-40	80-160-260
Aztreonam	3.3 mg/ml	20 %	Im	10-20-40	80-160-260
Cefalotin	2.5 mg/ml	20 %	Im	20-40-80	160-320-520
Cefalexine	90 mg/ml	20 %	PO	0.05-0.5-5	100-150-250
Cefaclor	90 mg/ml	20%	PO	0.05-0.5-5	100-150-250
Cefadroxil	90 mg/ml	20%	PO	0.05-0.5-5	100-150-250
Cefatrizine	90 mg/ml	20 %	PO	0.05-0.5-5	100-150-250
Cefamandole	2.5 mg/ml	20%	Im	20-40-80	160-320-520
Acetoxyethyl-cefuroxime	90 mg/ml	20%	PO	0.05-0.5-5	100-150-250
Cefixime	90 mg/ml	20%	PO	0.05-0.5-5	50-100-250
Ceftibuten	90 mg/ml	20%	PO	0.05-0.5-5	50-100-250
Cefotaxime	2.5 mg/ml	20 %	Im	20-40-80	160-320-520
Ceftriaxone	2.85 mg/ml	20%	Im	20-40-80	160-320-520

Route = route of administration; Im = intramuscular; PO = oral; D I = dose given on the 1st day; D II = dose given on the 2nd day.

Table II. Clinical characteristics of the patients.

Patients	Age/Sex	Responsible drugs	Time elapsing between drug administration and onset of symptoms	Time interval between onset of symptoms and time of assessment	Route	Symptoms
1	14/M	Ax	1 day	30 days	PO	MR
2	25/F	Ax	-	30 days	PO	U/Ang
3	33/F	B	2 days	10 years	PO	MR
4	28/F	Ax	5 days	1 year	PO	MR
5	28/F	B	-	1 year	PO	MR
6	40/F	B	12 hours	16 years	PO	U/Ang
7	29/F	Am	8 hours	-	PO	U/Ang + MR
8	62/F	Am	-	20 years	IM	MR
9	21/F	Am Ax	12 hours -	3 months	PO PO	MR MR
10	42/F	Ax	-	6 years	PO	E + D
11	44/F	B	2 days	-	PO	U/Ang + MR
12	19/M	Am B	1 day -	1 year 1 year	PO PO	U/Ang MR
13	17/F	Am Ax	8 hours 1 day	1 year 1 year	PO PO	U/Ang U/Ang
14	60/M	B Ax	- -	12 years 3 years	PO PO	E + F U/Ang
15	22/M	B	4 days	2 years	PO	U/Ang + MR
16	64/F	B	-	2 months	PO	MR
17	72/F	Am	2 days	4 years	PO	E
18	25/M	Ax	-	21 years	PO	E
19	25/F	Ax	-	2 years	PO	U/Ang
20	34/M	Ax Am	2 hours 4 hours	3 years 3 years	PO PO	E U/Ang
21	30/F	Ax	-	3 years	PO	U/Ang
22	52/F	Am Ax	3 days -	30 years 1 year	IM PO	MR MR
23	38/F	Ax	7 days	2 years	PO	MR
24	32/F	Am	4 hours	5 years	PO	E
25	40/F	Ax	-	1 year	PO	U/Ang
26	38/F	Am Ax B	5 hours - -	10 years 9 years 2 years	PO PO PO	U/Ang U/Ang MR
27	40/F	Ax	5 hours	1 year	PO	U/Ang

M = male; *F* = female; *Ax* = amoxicillina; *Am* = ampicillina; *B* = bacampicillin; *PO* = per os; *IM* = intramuscularly; *MR* = maculopapular rash; *U/Ang* = urticaria/angioedema; *E* = erythema; *D* = dyspnoea; *F* = fever; *Am* = ampicillin; *Ax* = amoxicillin; *B* = bacampicillin
- = unknown.

allergy to penicillin; this is probably due to the fact that T lymphocytes also recognise other epitopes of the penicilloyl group.

The diagnosis of delayed-type allergy to aminopenicillins has been made on the basis of the positivity of patch tests and of the negativity of skin tests and of the measurement of specific IgE in all

patients. The histological and immunochemical features of the biopsies from patch tests are typical for a cell-mediated reaction. In a recent review (21), the role of T cell subpopulations in the pathogenesis of delayed drug hypersensitivity reactions has been well clarified. CD4⁺ T lymphocytes are mainly involved in the pathogenesis of maculoapular

Table III. Oral and intramuscular challenge test results.

Patients	Negative oral challenge tests	Negative intramuscular challenge tests	Positive challenge tests
1	PV/ Cex/ Cxi	PG/ Pi/ M/ I/ A/ Cux	
2	PV/ Cex/ Ccl/ Cxi	PG/ Pi/ M/ I/ A/Cux	
3	PV/ Cex/ Cft/ Cdx	PG/ Pi/ Ti/ I/ A/Cux/ Cxo	
4	PV/ Cex/ Ccl/ Cft/ Cdx/ Ctr	PG/ Pi/ Ti/ I/ A/Cxo	
5	PV/ Cex/ Cft/ Cdx	PG/ Pi/ Ti/ I/ A/Cxo	
6	Cxi	I/A	
7	PV/ Cxi / Ccl/ Ctr	PG/ Pi/ I/ A/ Cux/ Cfm/ Cxo	Cex/Am
8	Cft	I/A	Cex
9	PV/ Cex/ Cft/ Cdx	PG/ I	
10	PV/ Cex/ Cxi/ Cdx	PG/ Pi/ A/ Cxo	
11	PV/ Cex/ Cxi/ Ctr	PG/ Pi/ I/ A/ Cxo	B
12	PV/ Cex/ Cxi/ Ccl/ Cdx	PG/M/ I/ A/ Cux	B
13	PV/ Cxi/ Cdx	Pi/ M/ I/ A/ Cux	B
14	PV/ Cex/ Cft/ Cfd	I/ A	
15	PV/ Cex/ Cft/ Crx	Ti/ I	
16	Cft	I/A	
17	Cft	I/ A	
18	Ccl/ Crx/ Cft/ Cpx	I/ A/	
19	PV/ Cex/ Ccl/ Cxi	PG/ M/ Pi/ I/ A/ Cux	
20	Cex/ Crx/ Cft/Ccl	I/ A/ Cxo	
21	PV/ Cex/ Ccl/ Crx/ Cft/ Cpx	Pi/ I/ A/ Cxo	
22	Crx/ Cft	I/ A	
23	Cex/ Crx/ Cft	Pi/ I	
24	PV/ Ccl/ Crx / Cft/ Cpx	Pi/ A/ I/ Cxo	
25	PV/ Ccl/ Crx/ Cft/ Cex	A	
26	Cex/ Ccl/ Crx/ Cft	I	
27	PV/ Cft/ Crx/ Ccl	I/ A/ Cfp	Cex

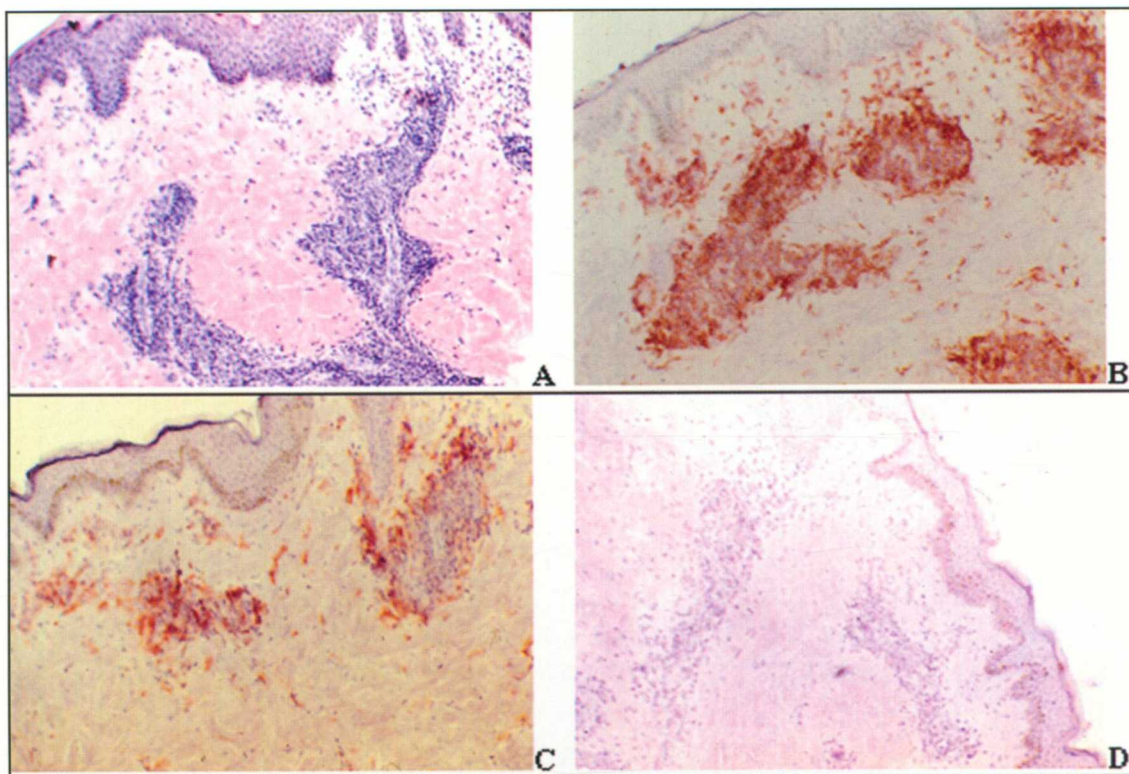
A = aztreonam; Am = ampicillin; Ax = amoxicillin; B = bacampicillin; Ccl = cefaclor; Cdx = cefadroxile; Cex = cefalexin; Cfd = cefradine; Cfm = cefamandole; Cfp = cefepime; Cft = ceftibuten; Cpx = cefpodoxima; Crx = acetoxyethyl-cefuroxime; Ctr = cefatrizine; Cux = cefuroxime; Cxi = cefixime; Cxo = ceftriaxone; I = imipenem; M = mezlocillin; PG = penicillin G; Pi = piperacillin; PV = penicillin V; Ti = ticarcillin.

exanthemas: CD4⁺ T lymphocytes can kill autologous keratinocytes and can express important mediators of cell-mediated cytotoxic reactions, such as perforin and granzyme B. CD8⁺ T lymphocytes are instead involved in bullous reactions. Our results, with a prevalence of a CD4⁺ T cell infiltrate do agree with other reports in literature that underline the role of CD4⁺ T lymphocytes in the pathogenesis of delayed drug reactions (22-23).

Patch tests represent a specific diagnostic tool with a high negative predictive value (98.5%) to identify alternative drugs that can be safely

administered to patients with β -lactam allergy. They should always be carried out together with skin tests and measurement of specific IgE in serum with a broad variety of molecules (PPL, MDM, penicillin G, penicillin V, ampicillin, amoxicillin, piperacillin, ticarcillin, imipenem, aztreonam, cephalixin, cefaclor, ceftriaxone, ceftibuten and other cephalosporins) in order to have a clear pattern of cross-reactivities and specificities for each patient.

Oral and parenteral tolerance challenge tests with other β -lactams let us confirm negativity of patch tests and identify alternative molecules. In fact, patch tests

Fig. 1. Skin biopsy specimens.

A) Skin biopsy microphotograph showing a dense mononuclear cell infiltrate around blood vessels (H and E; 200x). B-D) Immunohistochemical analysis. The vast majority of mononuclear cells are CD3 positive (B) and express CD4 (C) whilst are CD8 negative (D) (Avidin-biotin-peroxidase method; C and D, 100 x; B, 200x).

do not have a negative predictive value of 100% and challenge tests let us assess tolerance of molecules.

Our patients could tolerate natural and semisynthetic penicillins (except aminopenicillins), monobactams and carbapenems. We paid particular attention to tolerance challenge tests performed with aminocephalosporins that share the same α -amino SC which is responsible for allergic reactions to aminopenicillins and for the possible cross-reactivity with aminocephalosporins.

In our study, 3 patients out of 20 who underwent tolerance challenge tests with aminocephalosporins could not tolerate cephalexin, while the other aminocephalosporins were well tolerated. Such results suggest that cross reactivity among aminopenicillins and aminocephalosporins is not frequent (17-18) if we consider that they share the same SC (19). This can be probably explained by the fact that other parts of the molecules are necessary to form the antigenic epitopes. Only 1 patient out

of 3 with a positive OCT with cephalexin had a positive patch test with the same drug; therefore patch tests with cephalexin seemed to have a poor negative predictive value. At the end of the allergological work-up, we forbade our patients to use aminopenicillins and aminocephalosporins (cephalexin, cefaclor, cefradine, cefadroxil, cefatrizine) because of the possible cross-reactivity and we could recommend the use of all other β -lactams and, first of all, of penicillin.

In the past, patients allergic to one or more β -lactam drugs were told to avoid all the molecules of the group. In case of aminopenicillin allergy, this could lead to the avoidance of a great number of drugs (penicillins, carbapenems, monobactams and cephalosporins) with a broad antibacterial activity and good clinical tolerance.

On the basis of previous studies (11, 20) and of our data, delayed allergy to aminopenicillins must be considered a well-defined nosologic entity

characterised by the following main findings: patch test positivity with only aminopenicillins; a maculopapular rash and/or delayed-appearing urticaria are the most typical symptoms, arising a few hours or days after drug administration; cross-reactivity with aminocephalosporins is usually absent, or it is limited to cephalexin in our study; all the β -lactams, other than aminopenicillins (and cephalexin) were well tolerated.

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