

Natural evolution of skin test sensitivity in patients allergic to β -lactam antibiotics

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Background: Subjects with immediate reactions to penicillins and positive skin test responses may lose sensitivity if penicillin is avoided. The longer the interval between the reaction and the skin test, the greater the likelihood of having a negative result.

Objective: We sought to study prospectively the evolution of skin test sensitivity in a group of subjects allergic to penicillin with positive skin test responses to different penicillin determinants.

Methods: Skin tests were performed with major and minor determinants of benzylpenicillin (BPO/MDM), amoxicillin (AX), and ampicillin at the initial evaluation and repeated 1, 3, and 5 years later if the responses were still positive. Subjects were divided into 2 groups. Group A consisted of patients with a positive skin test response to benzylpenicilloyl or minor determinant mixture, and group B consisted of those with a selective response to amoxicillin and good tolerance to benzylpenicillin.

Results: In group A ($n = 31$) after 1 year, 25 patients continued to have positive responses and 6 began to have negative responses; after 3 years, 18 continued to have positive responses, 5 began to have negative responses, and 2 were lost to follow-up; and after 5 years, 12 continued to have positive responses, 5 began to have negative responses, and 1 was lost to follow-up. In group B ($n = 24$) 12 had positive responses, and 12 had negative responses after 1 year; 6 had positive responses, 5 had negative responses, and 1 was lost to follow-up after 3 years; and no patients had positive responses, 5 had negative responses, and 1 was lost to follow-up after 5 years. Survival analysis showed significant differences between groups (log-rank test = 12.8; $P < .0003$).

Conclusion: Patients with a selective response to amoxicillin tended to lose sensitivity faster than those who responded to several penicillin determinants, supporting the existence of at least 2 distinct types of IgE response in patients allergic to β -lactam. (*J Allergy Clin Immunol* 1999;103:918-24.)

Key words: Skin test, penicillin allergy, natural evolution, selective reaction

Subjects in whom IgE-mediated hypersensitivity responses to penicillin or its derivatives develop generally have positive skin test responses and/or RAST results caused by the presence in their skin of mast cells sensitized with penicillin-specific IgE antibodies^{1,2} or IgE antibodies in their serum.³ The most sensitive method for diagnosing patients who are allergic to penicillin is by using skin tests with major and minor determinants from benzylpenicillin.⁴ The RAST method, although correlating highly with skin tests,⁵ has proved to be less sensitive and not valid for minor determinants. The benzylpenicilloyl (BPO)-specific RAST elicits positive results in 60% to 95% of patients with a positive skin test response to BPO.⁴ Because selective allergic reactions to semisynthetic penicillins were described by our group⁶ and many others,⁷⁻¹⁰ it has been accepted that minor determinants of amoxicillin and other penicillin determinants should be used in skin tests.

Detection of IgE antibodies in the skin or serum depends on the time interval between the reaction and the evaluation. Different studies have shown that the longer the interval, the lesser the possibility of detecting IgE antibodies.^{1,11-14} Subjects with a history of penicillin allergy may have negative skin test responses for several reasons, including lack of skin test responsiveness or lack of adequate penicillin determinants for testing. However, the most common reason is loss of skin test sensitivity, particularly in cases evaluated some time after the occurrence of the reaction. This loss of sensitivity varies from case to case, but no sufficient studies have been carried out to examine it. The reason for the variability in the skin test response may be genetic or environmental because uncontrolled or hidden contact with β -lactams can occur, which could maintain sensitization.¹⁵⁻¹⁸

In this study we followed a group of 55 subjects who had an immediate reaction to different β -lactams and positive skin test responses to at least 1 penicillin derivative, including major and minor determinants of benzylpenicillin (BP) and minor determinants of amoxicillin (AX) and ampicillin (AMP). Patients were divided into 2 groups: those in whom a positive response to 1 or more penicillin determinants, including BPO and/or minor determinant mixture (MDM), developed (group A) and those with a selective response to AX (group B). Results

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Abbreviations used

AMP:	Ampicillin
AX:	Amoxicillin
AXO-PLL:	Amoxicylloyl-poly-L-lysine
BP:	Benzylpenicillin
BPO:	Benzylpenicilloyl
BPO-PLL:	Benzylpenicilloyl-poly-L-lysine
MDM:	Minor determinant mixture

indicate that the patients who had a selective reaction to AX tended to lose sensitivity faster than patients with positive responses to several penicillin determinants.

METHODS

Subjects

All patients who came to our clinic as a consequence of having had an immediate allergic reaction to a penicillin derivative by the oral or parenteral routes were eligible for inclusion in the study. Those with a positive skin test response to at least 1 of the penicillin determinants mentioned below were followed. To avoid any inadvertent contact during the follow-up period, we excluded those patients potentially exposed to penicillins, such as health care workers, pharmacists, veterinarians, and people working in chemical factories where penicillins are present. In addition, those subjects who had unexplained skin symptoms during the follow-up period or who may have had an inadvertent contact were withdrawn from the study.

On the basis of the patients' own descriptions, 2 clinical categories were established: anaphylaxis and urticaria/angioedema. Subjects were considered to have anaphylaxis if several of the following symptoms appeared: generalized erythema, systemic pruritus, dyspnea, gastrointestinal pain, nausea, vomiting, or hypotension. If symptoms were limited to the skin only with the appearance of large maculopapular areas plus systemic pruritus but none of the other symptoms described above, the case was classified as urticaria. Patients were diagnosed as having a selective response to AX if they reacted exclusively to AX determinants with negativity to BP determinants, had negative RAST results to benzylpenicilloyl-poly-L-lysine (BPO-PLL), and had good tolerance to BP administered parenterally or penicillin V administered orally.

Skin tests

The following determinants were used: BPO 5×10^{-5} mmol/L and MDM 2×10^{-2} mmol/L (both provided by Allergopharma, Merck, Darmstadt, Germany), AX 20 mg/mL (Beecham, Toledo, Spain), and AMP 20 mg/mL (Antibiotic SA, León, Spain). The same concentrations were tested in a control group of 20 patients and proved to be negative. Higher concentrations gave a false-positive response, as reported by others.^{9,19} Skin tests were made by the skin prick method, and if responses were negative, intradermal tests were carried out. Responses were classified as positive or negative as previously described.²⁰ In the skin prick tests a wheal larger than 2 mm with a negative response to the control saline was considered positive. In the intradermal test the wheal area was marked initially and 20 minutes after testing, and an increase in diameter greater than 3 mm was considered positive. To follow the decline in specific IgE antibodies by skin testing, we only included patients who had initially positive skin test responses to at least 1 of the haptens tested. Skin tests were repeated with the same haptens after 1, 3, and 5 years. If the skin test response became negative, it was no longer repeated and considered as loss of sensitivity.

Subjects were divided into 2 categories. Group A consisted of

patients who had positive skin test responses to BPO or MDM, and group B consisted of patients who had positive skin test responses to AX or AMP and negative skin test responses to both BPO and MDM. In addition, subjects included in group B had to have good tolerance to BP in a controlled challenge. When the subjects' responses became negative to the 4 conjugates tested, they were then considered to be skin test negative.

Serum total and specific IgE antibodies

Total IgE antibodies were measured by CAP (Pharmacia, Uppsala, Sweden). Specific IgE antibodies were measured by RAST to BPO-PLL and amoxicylloyl-poly-L-lysine (AXO-PLL) as described.²¹ In brief, in each sera RASTs were performed in duplicate and to BPO-PLL, AXO-PLL, and PLL alone, and results were expressed as the percentage of radiolabeled anti-IgE uptake. The value given by PLL was then subtracted. Blood samples were drawn at the moment the patients were evaluated, and a serum sample was obtained and kept frozen at -20°C until assayed. All samples were made in parallel, and values were considered positive if they were higher than 2.5, which was the mean $+ 2$ SD²² of the negative control group. Sera from the same negative controls used for skin testing were also used as controls to establish the cut-off point of the RAST assay.

Statistical analysis

Comparison of age between the patients was made by *t* test for independent groups, and the drugs implicated in the reactions were compared by using chi-square analysis. The evolution of skin test sensitivity was analyzed by survival analysis. Comparison of total IgE levels with the specific IgE values in the 2 groups was made by correlation analysis (Pearson coefficient). All the analyses were performed by using the SPSS statistical program.

RESULTS

Fifty-five patients in whom an immediate allergic reaction to a penicillin derivative developed and who had positive skin test responses to at least 1 penicillin determinant were included in the study. Thirty-one had positive skin test responses to BPO and/or MDM, and these patients formed group A. The clinical characteristics of these patients and the drug eliciting the reaction are presented in Table I. Of these there were 16 men and 15 women, with an age range of 29 to 68 years (47.74 ± 12.58), 18 of whom (58.1%) had anaphylaxis, and 13 (41.9%) of whom had urticaria. The drugs involved in treatment of the patients with anaphylaxis were AX in 10 (55.6%), BP in 3 (16.7%), nonidentified penicillin in 4 (22.2%), and AMP in 1 (5.6%), and those involved in the treatment of the subjects with urticaria were nonidentified penicillin in 7 (53.8%), AX in 4 (30.8%), and AMP in 2 (15.4%). Group B was composed of 24 patients with a selective response to AX. Of these there was 12 men and 12 women, with an age range of 22 to 65 years (35.75 ± 10.37), 20 (83.3%) of whom had anaphylaxis, and 4 (16.7%) of whom had urticaria (Table II). There were no significant differences in age between both groups.

The results of the immunologic tests are shown in Tables III and IV. In Group A 20 (64.5%) patients had positive skin test responses to BPO, 18 (58.1%) to MDM, 14 (45.1%) to AX, and 12 (38.7%) to AMP. RAST evaluation showed 14 patients (45.1%) had positive responses

TABLE I. Age, sex, diagnosis and drug involved in the reaction of patients from group A

Patient	Age (y)	Sex	Diagnosis	Drug
1-A	62	M	Anaphylaxis	AMP
2-A	52	M	Anaphylaxis	AX
3-A	32	M	Anaphylaxis	AX
4-A	47	M	Anaphylaxis	AX
5-A	52	M	Anaphylaxis	AX
6-A	53	M	Anaphylaxis	AX
7-A	37	M	Anaphylaxis	AX
8-A	33	M	Anaphylaxis	AX
9-A	47	M	Anaphylaxis	AX
10-A	52	F	Anaphylaxis	BP
11-A	36	F	Anaphylaxis	Penicillin
12-A	59	F	Anaphylaxis	Penicillin
13-A	56	M	Anaphylaxis	Penicillin
14-A	60	M	Anaphylaxis	Penicillin
15-A	54	F	Anaphylaxis	AX
16-A	31	M	Anaphylaxis	AX
17-A	62	M	Anaphylaxis	BP
18-A	54	F	Anaphylaxis	BP
19-A	57	F	Urticaria	AMP
20-A	30	M	Urticaria	AMP
21-A	37	F	Urticaria	AX
22-A	53	F	Urticaria	AX
23-A	29	M	Urticaria	AX
24-A	31	F	Urticaria	AX
25-A	55	F	Urticaria	Penicillin
26-A	54	F	Urticaria	Penicillin
27-A	32	F	Urticaria	Penicillin
28-A	62	M	Urticaria	Penicillin
29-A	68	F	Urticaria	Penicillin
30-A	67	F	Urticaria	Penicillin
31-A	52	F	Urticaria	Penicillin

TABLE II. Age, sex, diagnosis and drug involved in the reaction of patients from group B

Patient	Age (y)	Sex	Diagnosis	Drug
1-B	39	M	Anaphylaxis	AX
2-B	33	M	Anaphylaxis	AX
3-B	35	F	Anaphylaxis	AX
4-B	34	M	Anaphylaxis	AX
5-B	33	F	Anaphylaxis	AX
6-B	29	F	Anaphylaxis	AX
7-B	25	M	Anaphylaxis	AX
8-B	37	F	Anaphylaxis	AX
9-B	32	F	Anaphylaxis	AX
10-B	37	M	Anaphylaxis	AX
11-B	32	F	Anaphylaxis	AX
12-B	31	F	Anaphylaxis	AX
13-B	42	M	Anaphylaxis	AX
14-B	36	F	Anaphylaxis	AX
15-B	24	M	Anaphylaxis	AX
16-B	22	F	Anaphylaxis	AX
17-B	48	F	Anaphylaxis	AX
18-B	65	M	Anaphylaxis	AX
19-B	36	M	Anaphylaxis	AX
20-B	38	M	Anaphylaxis	AX
21-B	59	F	Urticaria	AX
22-B	32	F	Urticaria	AX
23-B	40	M	Urticaria	AX
24-B	19	M	Urticaria	AX

es to BPO and 10 (32.3%) to AX. Although AX was the drug most frequently involved (45.1%), the determinants inducing most positive responses were those derived from BP, which indicates that this is a cross-reacting group. In group B, however, all the patients had negative skin test responses to determinants from BPO and MDM and positive responses to AX only, but 12 of these (50%) had positive responses to AMP also (Table IV). RAST evaluation in this group showed that only 7 patients (29.2%) had positive responses to AXO, indicating that the sensitivity of the in vitro method in subjects with positive test responses to AX is less than 50%. The Pearson correlation coefficient was 0.1 when total IgE values were compared with RAST to BPO-PLL in both groups A and B. When we compared total IgE with RAST response to AXO-PLL, the values were 0.08 in group A and 0.1 in group B. In all instances these values were not significant.

The results of the skin tests over the follow-up period of 5 years, during which a total of 5 patients were lost, showed that in group A (n = 31) after 1 year, 25 (80.6%) patients continued to have positive responses and 6 (19.4%) began to have negative responses; after 3 years, from all those patients continuing to have positive responses (n = 25), 2 (8%) were lost to follow-up, 18 (72%) had positive responses, and 5 (20%) had negative

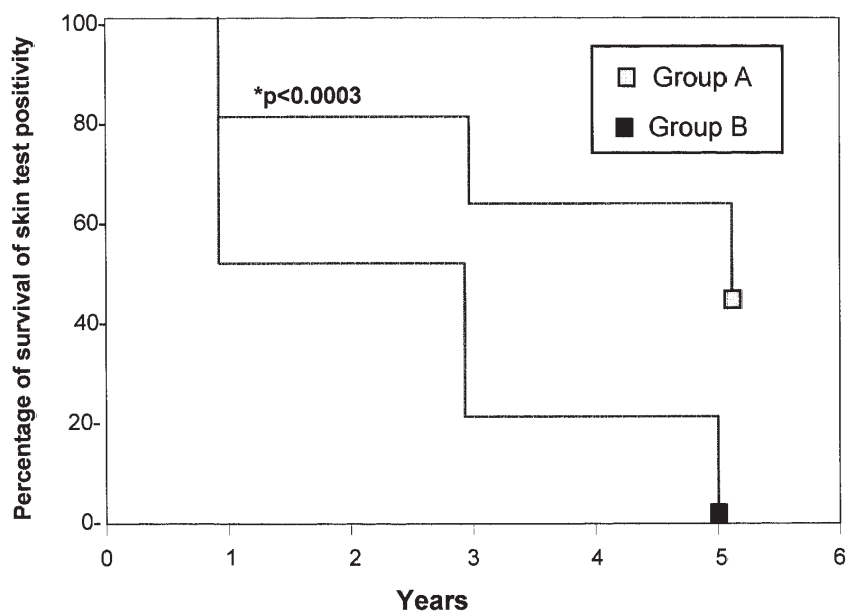


FIG 1. Survival analysis of switch to negative for skin test responses in group A and group B.

TABLE III. Skin test responses to BPO, MDM, AX, and AMP and total IgE levels and RAST results to BPO-PLL and AXO-PLL in patients from group A

Patient	Skin tests				Total IgE	RAST	
	BPO	MDM	AX	AMP		BPO-PLL	AXO-PLL
1-A	+	—	—	—	1000	4.2	0.9
2-A	—	+	+	+	90	0.1	0.12
3-A	—	+	+	+	22	0.7	1.0
4-A	+	—	+	+	100	1.5	3.3
5-A	+	—	—	—	38	28.6	3.0
6-A	—	+	+	+	210	7.3	7.7
7-A	—	+	+	+	250	2.2	1.4
8-A	+	+	+	+	120	0.1	0.6
9-A	+	+	+	—	35	6.3	1.1
10-A	—	+	—	—	97	0.2	0.5
11-A	+	—	—	—	59	20.0	3.5
12-A	+	+	—	—	66	1.9	0.6
13-A	+	—	—	—	40	16.12	4.4
14-A	+	—	—	—	35	0.2	0.1
15-A	—	+	+	+	432	1.08	0.5
16-A	+	—	+	+	120	7.2	9.1
17-A	+	+	+	+	37	3.4	1.3
18-A	+	—	—	—	92	1.4	0.5
19-A	+	—	—	—	53	5.7	5.9
20-A	—	+	+	+	100	0.1	0.1
21-A	—	+	+	+	72	1.1	0.2
22-A	+	+	—	—	120	2.7	1.6
23-A	—	+	+	+	210	0.3	0.2
24-A	—	+	+	—	85	3.2	2.8
25-A	—	+	—	—	160	3.0	1.5
26-A	+	—	—	—	25	1.3	0.6
27-A	+	+	—	—	13	0.2	0.7
28-A	+	—	—	—	57	10.1	6.5
29-A	+	—	—	—	88	3.1	3.8
30-A	+	—	—	—	95	1.6	0.2
31-A	+	+	—	—	32	1.2	0.7

TABLE IV. Skin test responses to BPO, MDM, AX, and AMP and total IgE levels and RAST to BPO-PLL and AXO-PLL in patients from group B

Patient	Skin tests				Total IgE	RAST	
	BPO	MDM	AX	AMP		BPO-PLL	AXO-PLL
1-B	—	—	+	—	232	0.2	0.1
2-B	—	—	+	+	71	0.1	5.3
3-B	—	—	+	+	43	1.1	2.1
4-B	—	—	+	+	25	0.2	0.3
5-B	—	—	+	+	359	0.6	1.3
6-B	—	—	+	—	57	2.1	9.3
7-B	—	—	+	+	101	0.3	5.0
8-B	—	—	+	—	238	0.9	0.1
9-B	—	—	+	+	15	1.3	1.9
10-B	—	—	+	+	37	2.2	5.9
11-B	—	—	+	+	470	2.3	1.3
12-B	—	—	+	—	17	0.3	0.6
13-B	—	—	+	—	95	1.2	2.6
14-B	—	—	+	—	38	0.2	0.7
15-B	—	—	+	+	157	0.3	0.2
16-B	—	—	+	—	224	0.3	0.2
17-B	—	—	+	+	60	0.1	0.1
18-B	—	—	+	—	361	0.2	0.7
19-B	—	—	+	+	128	0.1	5.3
20-B	—	—	+	—	369	0.5	3.7
21-B	—	—	+	+	10	0.2	0.1
22-B	—	—	+	—	59	0.9	0.1
23-B	—	—	+	—	87	0.2	0.7
24-B	—	—	+	—	113	0.1	0.3

responses; and after 5 years from all those continuing to have positive responses ($n = 18$), 1 (5.6%) was lost to follow-up, 12 (66.7%) had positive responses, and 5 (27.8%) had negative responses. When we evaluated group B ($n = 24$), we found that after 1 year 12 (50%) patients continued to have positive responses, and 12 (50%) had negative responses; after 3 years from all those continuing to have positive responses ($n = 12$), 6 (50%) had positive responses, 5 (41.7%) had negative responses, and 1 (8.3%) patient was lost to follow-up; and after 5 years ($n = 6$), no patients had positive responses (0%), 5 (83.3%) had negative responses, and 1 patient was lost to follow-up (16.7%).

The results of the survival analysis are presented in Fig 1. There was a statistically significant difference between the groups (log-rank test = 12.80; $P < .0003$), indicating that the interval of negativization was not the same.

DISCUSSION

In this study we followed prospectively the evolution of skin test sensitivity in 2 groups of subjects with an allergic reaction to a β -lactam derivative and in whom a type I reaction was demonstrated by the presence of specific skin sensitizing IgE antibodies to 1 or more penicillin determinants. The same protocol for evaluation and immunologic tests was used throughout the study. Although a number of studies indicate that subjects with penicillin-induced allergic reactions gradually lose their

sensitivity, these are mainly based on a past positive history, and figures vary from 15% to 75%.^{1,11,13,23-25} A prospective study in a group of patients with a definite positive skin test response would therefore seem more reliable to evaluate this loss of sensitivity.

The immune response to penicillin is heterogeneous, and studies have shown different patterns of skin responses to different penicillin determinants.^{1,13,23-24} The use of minor determinants of AMP, AX, cloxacillin, and methicillin may increase the number of positive skin test responses in subjects allergic to penicillins in 5% to 45% of cases.^{2,7,26,27} Furthermore, in subjects allergic to penicillin a selective group with positive skin test responses only to AX and good tolerance to BP has been identified.⁶ We therefore divided our study patients into 2 groups: those with an allergic reaction to a penicillin derivative and who had positive skin test responses to BPO and/or MDM, some of whom also responded to semisynthetic penicillin determinants (group A), and those with a selective response to AX (group B).

In group A all patients had positive skin test responses to the BP determinants BPO or MDM, although BP itself was not usually involved in the reaction, and 45.1% had positive responses to AX and/or AMP. These characteristics have also been reported by others in different populations.¹⁰⁻¹² BPO was also the most recognized hapten in *in vitro* IgE evaluation, and this has also been reported and confirmed by RAST inhibition studies.^{10,22} In group B, however, all patients had positive responses to AX and negative responses to BP determinants with good toler-

ance to BP, indicating the selectivity of this group. Fifty percent of this group also responded to AMP by skin testing, showing that cross-reactivity between the side chains of AMP and AX exists, as previously reported by our group.²⁸

Studies concerning the evolution of sensitivity to penicillin are few, and not all are totally comparable.^{1,11,29,30} Finke et al²⁹ found that the frequency of positive skin reactions in patients allergic to penicillin fell from 77% 3 months after the reaction to 25% after 5 to 10 years. Sullivan et al¹ found that in a group of subjects with a positive history to penicillin, 73% continued to have positive responses within 1 year of the reaction, 57% between 1 and 10 years, and 22% 10 years or more after the reaction. Although the studies are not totally comparable, these data are similar to those of our group A. Other studies have also shown variable results.^{11,30} Some investigators have tried to answer these questions by following patients and repeating the skin tests.^{3,25} Kraft et al³ found that 23% of the patients studied had negative results within 12 months and 41% after more than 1 year, but the number of subjects was very small, and they were divided in different groups. Chandra et al²⁵ found that 33.3% of the patients with previously positive test responses (skin and RAST) had negative responses after 1 year.²⁵ The results of our study show that although no patient in group B had positive responses after 5 years, 66.7% of the patients in group A still had positive responses after this same period, indicating that there were important differences between the groups. In a recent prospective study carried out by Patriarca et al,¹⁴ approximately 50% of patients had positive responses after 3 years, and around 30% had positive responses after 5 years. These are figures similar to our group A, indicating that both groups are similar and that a group similar to our group B was not present. In our study the survival analysis showed that there were significant differences between both groups, thus confirming the existence of at least 2 different groups.

An interesting question is the possibility of maintaining sensitization by doing skin tests. Although there is evidence that results can become positive after contact with penicillin, this has been mainly related with the therapeutic administration of the drug and therefore at a high concentration.^{11,31} In a study carried out by our group, it has been shown that resensitization may also occur after nontherapeutic exposure in subjects allergic to penicillin in whom negative skin test and RAST results develop,¹⁵ although the quantity of drug to which patients were exposed was higher than the quantities used in skin testing. The possibility for becoming resensitized after skin testing would therefore seem quite unlikely.^{1,13,23}

In summary, we carried out a prospective 5-year study of the natural evolution of skin test sensitivity in 2 groups of subjects allergic to penicillin. Those patients with a selective response to AX switched from positive to negative responses sooner than those with reactivity to several penicillin determinants. This indicates that these 2

populations are different and well characterized not only in their clinical and immunologic response but also in the natural evolution of their sensitivity.

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