

*Nonimmediate reactions to betalactams: prevalence and role of the different penicillins

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In patients treated with penicillins, adverse cutaneous reactions can occur within minutes or may take several days to develop. IgE antibody-mediated reactions are well documented, but other mechanisms may also be involved. In particular, nonimmediate reactions have not been studied extensively, and the purpose of the present work was to establish the incidence of such reactions among a large group of patients and to study the penicillins involved. A total of 380 subjects with a history of a cutaneous reaction following administration of a penicillin antibiotic was included in the study. Skin tests and specific IgE measurements (RAST) were carried out using various penicillins and penicillin-related reagents, and patients were also challenged with various penicillins. In some patients with delayed skin test responses, skin biopsies were carried out. The tests confirmed that 74 subjects (19.4% of total investigated) had suffered a cutaneous reaction to a penicillin derivative, and 29 of these subjects (7.6% of total or 39% of confirmed) showed evidence of having suffered a nonimmediate reaction. The latter group were identified by giving a positive delayed direct challenge, and in 65% of the cases a delayed skin test response was detected. In most cases, these responses were to amino penicillins. Skin biopsies showed a lymphomonocytic cell infiltrate. Nonimmediate reactions to penicillins are a reproducible phenomenon, suggesting that a specific mechanism is responsible. By direct challenge, 93% of responders were positive to amino penicillins (10.3% ampicillin, 82.7% amoxicillin), indicating a major role for these penicillins in nonimmediate reactions. The high percentage (65%) of subjects in this group who showed delayed skin test responses, taken together with the biopsy results, suggests that a lymphocyte-mediated reaction occurred. However, the possibility that other mechanisms may also have been involved cannot be ruled out.

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Penicillins have been associated with various types of adverse reactions (1). In some, an immunologic mechanism is clearly involved, as in IgE-mediated reactions (14) and immune hemolytic anemias (1, 2, 4), but this is not true of all penicillin-related reactions (1, 24, 25). Levine suggested that reactions to penicillin could be classified as immediate, accelerated, or delayed, according to the time interval between administration of the drug and appearance of the reaction (14). Immediate reactions involving IgE antibody have been extensively studied, but the mechanisms involved in accelerated and delayed re-

actions are less well understood (25). In some cases, accelerated reactions show similarities to a serum-sickness-like syndrome except that neither IgE nor IgG has been shown to be involved (20).

In this paper, we have concentrated on subjects reporting cutaneous reactions, the commonest allergic response to penicillins (9). Cutaneous reactions can be categorized as urticaria and/or angioedema, exanthem, or contact eczema (17). Urticaria and angioedema are usually caused by specific IgE antibody (20, 25), and skin tests and RAST are useful diagnostic aids. This is not the case with exanthematic reactions (3, 9), and the mechanisms which induce these reactions have not been elucidated (7, 9, 12). Contact eczema is the best example of delayed-type hypersensitivity to betalactams (1, 15),

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and occupational exposure, particularly to semisynthetic penicillins in factories, is the most frequent cause (7, 16, 19). In this case, patch testing is considered the most sensitive method to confirm diagnosis. The contribution of cellular mechanisms to other types of adverse reactions caused by penicillins has not been investigated in depth (9).

Few data are available about the incidence or mechanism of nonimmediate reactions in subjects allergic to penicillins (9). In most cases, these reactions are thought to be caused by nonimmunologic mechanisms; therefore, subjects can safely tolerate the drugs on subsequent occasions (1, 9). However, some studies suggest that nonimmediate reactions can occur in penicillin-allergic subjects (5, 18) with consequences for future treatment.

We have studied a large population of subjects with a history of cutaneous reactions to penicillins in order to establish whether the original reaction was immediate or nonimmediate. Data on the prevalence of nonimmediate reactions, the responsible penicillins, and the selectivity of these responses with respect to the causative agent are presented.

Material and methods

Patient selection

All patients who attended the clinic because of a suspected reaction to a penicillin were included in the study. The period for evaluation was from 1987 to 1991. Reactions were classified as follows according to the patients' description of the symptoms:

- 1) urticaria, if maculopapular elevation of the skin appeared in different parts of the body
- 2) exanthem, if a maculopapular rash or diffuse reddening of the skin occurred
- 3) desquamative exanthem, if erythematous lesions progressed to desquamation
- 4) serum-sickness-like syndrome if, in addition to urticaria or exanthem, articular manifestations including joint swelling occurred.

Patients who gave a history of symptoms suggestive of anaphylactic reactions, even if they reported some of the above symptoms, were excluded from the study.

Skin tests

Intradermal skin tests were carried out using the following reagents: benzyl penicilloyl polylysine (BPO-PLL) and minor determinant mixture (MDM), prepared and used according to Blanca et al. (5). Benzyl penicillin (BP) (maximum concentration 10000 iu/ml), amoxicillin (AX), and ampicillin (AMP) were also used. The last two were used at 20 mg/ml. Skin test responses were read at 15 min and 48 h. All the determinants were tested in a group

of 40 negative controls with no history of allergy to penicillin.

Specific IgE antibody measurements

Specific IgE antibody measurements used the RAST system with BPO-PLL, amoxicilloyl polylysine (AX-PLL), and ampicilloyl polylysine (AMP-PLL), as described by Blanca et al. (6).

Drug provocation

To confirm the types of reaction reported, the patients were challenged as follows. Up to 1 million units of BP was administered intramuscularly, and if a nonimmediate reaction appeared, phenoxy methyl penicillin (PV) up to 500 mg was administered orally. If neither an immediate nor a delayed reaction occurred, challenge with up to 500 mg of either AX or AMP was carried out 1 week later, also orally. When immediate reactions were confirmed by positive skin tests or RAST, subjects were not challenged. In all cases, where a nonimmediate response was suspected, a controlled challenge was carried out.

Skin biopsies

Skin biopsies were carried out as described by Dolovich et al. (10). Tissue samples were stained with hematoxylin and eosin. Direct immunofluorescence was used to detect deposits of IgG, IgM, and IgA and complement C₃.

Results

A total of 380 subjects (77% female 23% male) was selected on the basis of clinical history. A breakdown of their symptoms is shown in Table 1. Of the subjects, 73.4% reported urticaria and/or angioedema, 22.4% exanthem, 1.8% exanthem and/or erythema followed by desquamative lesions, and 2.4% symptoms suggestive of serum-sickness-like syndrome. AMP was the most frequent cause of desquamative lesions, but AX was the most frequent cause of all the other symptoms.

Skin tests in the negative control group produced two cases of immediate positive response, one to BPO and one to AMP, and one case of delayed positive response to AMP and AX.

The objective tests gave one or more positive responses in 74 subjects (19.4% of the total). Forty-five of these subjects were classified as having an immediate reaction to a penicillin on the basis of giving a positive skin test response within 15 min of testing or presence of IgE antibodies by RAST. The mean age was 42 years (range 14–68); 29 subjects were female and 16 were male. A total of 38 cases

Table 1. Clinical manifestations of participating subjects and number of cases for implicated drug

Clinical manifestations	BP	AX	AX-CLAV	Drugs AMP	CLX	PB	UNK	Percentage of patients
Urticaria and/or angioedema	73	111	16	32	10	6	31	73.4
Generalized exanthema	16	46	2	14	3	0	4	22.4
Desquamative lesions	1	2	1	4	0	0	0	1.8
Serum-sickness-like syndrome	2	3	1	2	0	1	0	2.4

BP: benzyl penicillin; AX: amoxicillin; AX-CLV: amoxicillin-clavulanic; AMP: ampicillin; CLX: cloxacillin; PB: penicillin benzathine; UNK: unknown.

developed urticaria, three generalized exanthema, and four only angioedema. There were 31 cases with a skin test positive to one or more of the determinants used. Results can be seen in Table 2. The BPO determinant was the most frequently positive (21 cases), followed by AX in 13 cases, AMP in 11 cases, and MDM in seven cases. In 19 cases, the skin tests were positive to only one determinant: to BPO in 16, to AX in two, and to MDM in one. In four cases, RAST was positive with skin test negative, three to BPO-PLL and one to AXO-PLL. Ten cases needed to be challenged to confirm an immediate response to penicillin, six to BP and four to AX, and the results are seen in Table 3. One of the patients who reported having had exanthema developed generalized erythema on the chest and abdomen 1 h after administration of 500 mg of PV, and another developed exanthema on the chest and face 10 min after taking 500 mg of PV (subject nos. 3 and 5 of Table 3). The third subject with exanthema was skin test positive to BPO.

Twenty-nine subjects were diagnosed as having suffered nonimmediate reactions by giving delayed responses to direct challenge tests.

The nonimmediate reaction group had a mean age of 44 years (range 17–69) and consisted of five men and 24 women. Nineteen of the subjects had given delayed skin test results (two positive to BP, AX, and AMP and 17 positive to AX and AMP), but 10 failed to respond even after 48 h. By direct challenge, two subjects had responded to PV and were not

challenged further, but 27 had tolerated BP and PV and responded only to either AMP (three subjects) or AX (24 subjects). Three subjects were not challenged due to other medical problems; in one case, a delayed skin test response to AX and AMP appeared, but in a subsequent evaluation the subject developed an immediate response after BP challenge and skin tests converted to positive BPO. Fig. 1 shows the percentage of subjects responding at different times after challenge. Most showed symptoms by 48 h, but three required 72 h. On challenge, responses occurred at between 6 and 72 h, with 72% of subjects responding in 24–48 h. Exanthema alone

Table 2. Results of immunologic tests on subjects with immediate response

Skin tests	No. of cases	Percentage
BPO, MDM, AX, AMP	2	6.4%
BPO, MDM, AX	1	3.2%
BPO	16	51%
MDM, AX, AMP	3	9.6%
MDM	1	3.2%
AX, AMP	4	12.9%
AX	2	6.4%
BPO, AX, AMP	1	3.2%
BPO, AMP	1	3.2%

BPO: benzyl penicilloyl; MDM: minor determinant mixture; AX: amoxicillin; AMP: ampicillin.

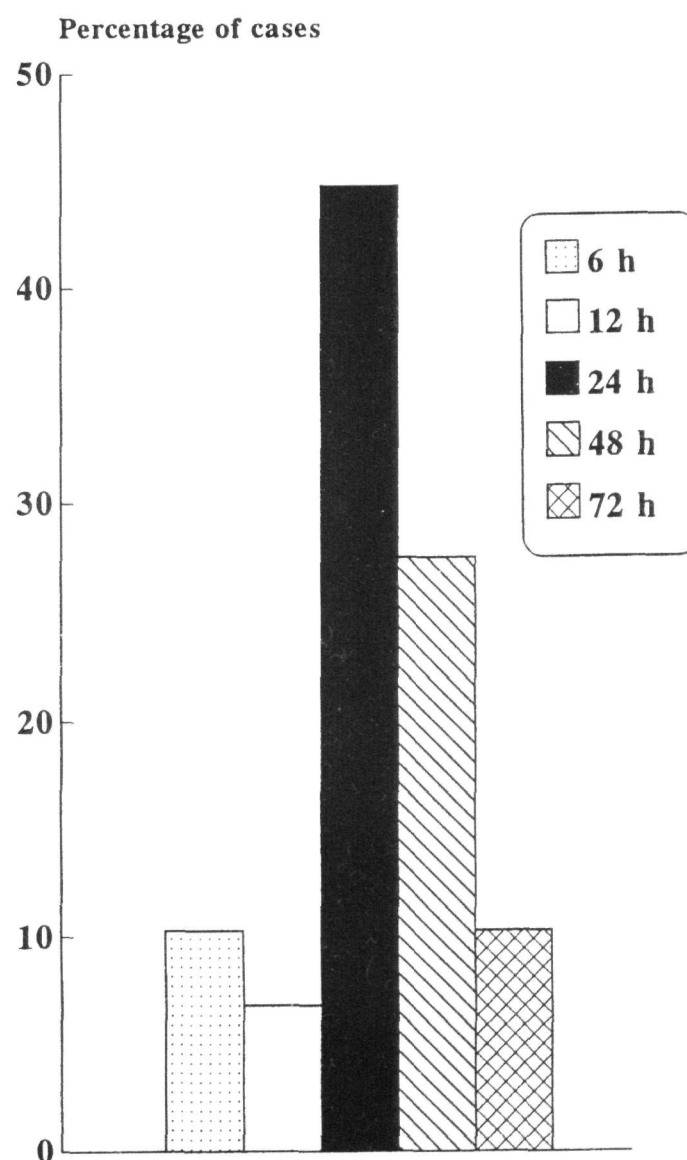


Fig. 1. Time interval between direct challenge and appearance of symptoms for nonimmediate reaction group.

or associated with desquamative manifestations or fever occurred in 79.3% of subjects (Fig. 2). This is in contrast to the symptoms reported for the initial reaction, where urticaria or angioedema predominated (73.4%) (Table 1). Nineteen subjects (65.5%) gave nonimmediate positive skin tests, and six skin biopsies showed a lymphocyte and mononuclear infiltrate but no immunoglobulins or complement, suggesting a type IV cell-mediated reaction.

Discussion

A total of 380 patients who reported suffering a cutaneous response to a penicillin were subjected to objective tests to confirm their allergy. In 74 cases, one or more of the tests were positive. Forty-five cases were classified as having an immediate reaction. The BPO determinant was involved in 67% of cases with an immediate reaction and was also the determinant that contributed alone to produce more positives (51%). These data confirm previous results reported by our group (5) and support findings that skin test positivity to BPO appears more frequently in cases with urticaria (11).

Although the percentage of the cases with positive skin tests was 68%, and when combined with those only RAST positive it increased to 77%, 23% needed a controlled challenge to confirm the diagnosis. Similar data have been previously reported by our group (5, 22). In 29 subjects, the results suggested that they had originally suffered a nonimmediate reaction. This is a prevalence of 7.6% in the total population evaluated and 39% of the cases evaluated as positive. A delayed response after direct challenge was used to define this group.

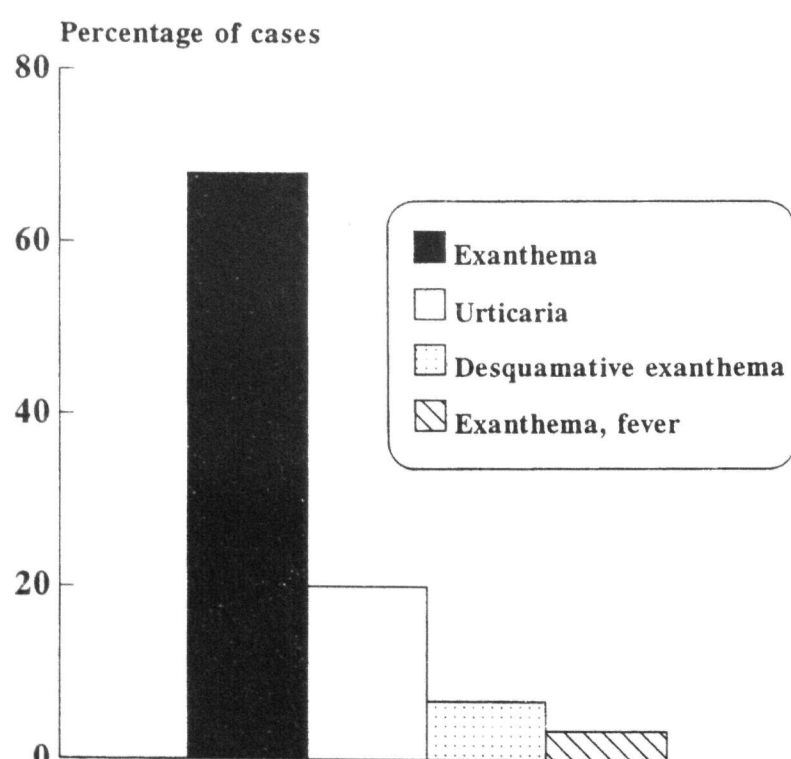


Fig. 2. Clinical symptoms presented by 29 subjects with non-immediate reaction when directly challenged.

Table 3. Results of challenge in group with immediate reactions and negative skin tests

Subject	Reaction induced after challenge
1.	Pruritus and urticaria in leg and abdomen 30 min after 1×10^6 BP injection
2.	Generalized erythema in chest and abdomen 1 h after 500 mg of PV
3.	Urticaria in leg 1 h after 1×10^5 of BP injection
4.	Pruritus and erythema in chest and neck 10 min after 500 mg of PV
5.	Exanthema in chest and face 10 min after 500 mg PV
6.	Facial and lip angioedema 1 h after 1×10^6 of BP injection
7.	Generalized erythema in legs and abdomen after 500 mg of PV
8.	Face and lips angioedema after 1×10^5 of BP injection
9.	Urticaria in abdomen and neck after 1×10^6 BP injection
10.	Angioedema in hands, neck, and face after 500 mg of PV

BP: benzyl penicillin; PV: phenoxymethyl penicillin.

Nineteen of 29 subjects (65.5%) with a non-immediate reaction developed a positive skin test response. These results indicate that skin testing does have a role in evaluating delayed reactions. Others have reported that amino penicillins are an important cause of nonimmediate reactions (8–10, 21, 23) and can give very selective responses (19, 21). In our study, all subjects with a positive skin test response responded to AX and AMP, but only two responded to BP. The ability of some penicillins to cause contact eczema more frequently than others seems to be related to their irritant capacity and lipophilicity. Thus, cloxacillin and bacampicillin are more potent sensitizers than benzyl penicillin (13). In some studies, 5–10% of patients treated with AMP had exanthematic reactions (15). In many instances, these symptoms were associated with an underlying disease such as infectious mononucleosis, influenza, and cytomegalovirus infections, and when this has resolved, the patient can tolerate AMP again. However, in some circumstances, subjects responded to a controlled challenge (5, 8, 21), suggesting that delayed-type hypersensitivity had developed (2, 9, 21).

Several mechanisms have been suggested as causing or being involved in nonimmediate reactions, but none have been conclusively shown to do or be so. Both penicillin and cephalosporins can give positive lymphocyte transformation tests (2, 12, 17, 19, 24), but although these have been associated with the appearance of nonimmediate reactions, they have also been reported in normal subjects (2, 19). Evidence for antibody-mediated mechanisms is not convincing (8, 18), and recent studies suggesting cytotoxic mechanisms need further evaluation (26).

In summary, in contrast to those of other studies (3, 15), our results indicate that penicillin-induced nonimmediate cutaneous reactions, including exanthema, are a reproducible phenomenon with a high prevalence (7.6% among history-positive subjects and 39% objectively confirmed). Additionally, in our study group, amino penicillins were the most fre-

quent cause of symptoms, and responses were selective for these penicillins.

Accordingly, we again stress the importance of using AX and AMP in addition to major and minor determinants of benzyl penicillin for skin testing and controlled studies. Further studies on the mechanism of these responses are underway.

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