

A diagnostic protocol for evaluating nonimmediate reactions to aminopenicillins

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Background: Maculopapular and urticarial rashes are nonimmediate manifestations common during aminopenicillin (AP) treatment, and the former often represent cell-mediated hypersensitivity.

Objectives: We sought to determine the significance and incidence of skin test reactions to APs in adults reporting adverse reactions during therapy with these β -lactams and, particularly, to evaluate the potential of patch tests, delayed-reading skin tests, and challenges in the diagnosis of nonimmediate reactions.

Methods: We used skin tests with penicilloylpolylysine, minor determinant mixture, benzylpenicillin, ampicillin, and amoxicillin, as well as patch tests with the last 3 drugs. We also performed *in vitro* assays for specific IgE and challenges with the suspect penicillin in subjects with nonimmediate reactions.

Results: Among the 144 patients reporting nonimmediate manifestations (mostly maculopapular rashes), delayed hypersensitivity was diagnosed in 62 on the basis of positive patch test and/or delayed intradermal test results and responses to challenges; negative reactions to challenges allowed us to reasonably exclude the possibility of allergy in 66 subjects, and the challenge confirmed that 1 patient had linear IgA bullous dermatosis. Definitive diagnoses could not be provided for the remaining 15 subjects, who had negative allergologic test results, because they did not consent to challenges. In 40 of 49 immediate reactors, a diagnosis of IgE-mediated hypersensitivity was made.

Conclusions: Both patch and intradermal tests are useful in evaluating nonimmediate reactions to APs. Positive patch test and delayed intradermal responses together indicate delayed hypersensitivity. Intradermal testing appears to be more sensitive than patch testing, but the pattern of positive delayed intradermal test responses and negative patch test responses needs further investigation because of false-positive cases. (*J Allergy Clin Immunol* 1999;103:1186-90.)

Key words: Ampicillin, amoxicillin, delayed hypersensitivity, maculopapular rash, intradermal test, nonimmediate reactions, patch test

Penicillins have been associated with various types of allergic reactions classifiable as immediate, accelerated,

Abbreviations used

AM:	Ampicillin
AP:	Aminopenicillin
AX:	Amoxicillin
BC:	Bacampicillin
BP:	Benzylpenicillin
MDM:	Minor determinant mixture
PPL:	Penicilloylpolylysine

or delayed according to the time interval between drug administration and onset.¹ Immediate reactions occur within the first hour after drug administration and are manifested clinically by urticaria and/or angioedema, rhinitis, wheezing, hypotension, or shock.^{2,3} Accelerated reactions occur 1 to 72 hours after drug administration, and delayed reactions take more than 72 hours to appear. This terminology may be simplified by defining all reactions occurring more than 1 hour after drug administration as nonimmediate. The main nonimmediate reactions are maculopapular rash, urticaria/angioedema, wheezing, interstitial nephritis, and serum sickness.^{2,3}

Immediate reactions involving IgE antibodies have been extensively studied, but until the mid-1980s, the mechanisms involved in nonimmediate reactions were not fully understood. Like late-onset urticarial eruptions, maculopapular rashes, which usually appear 2 days or more after therapy begins and are not associated with IgE antibodies, were thought to be delayed idiopathic drug reactions.^{2,3} Over the last decade, however, several investigators have come to the conclusion that these rashes often represent type-IV (cell-mediated) hypersensitivity, which is associated with positive patch test and/or delayed (ie, >6 hours after administration) intradermal test responses.⁴⁻¹⁰ In some cases biopsies have been performed on tested skin; histologic features similar to those of allergic contact dermatitis have been found,^{5-8,10} and challenges with the suspect drug have provoked delayed-onset skin rashes.^{5,6,8,9}

A few years ago, our group showed that over 50% of the patients who had experienced maculopapular reactions during aminopenicillin (AP) treatment had delayed hypersensitivity to the culprit drug.¹¹ Although the percentage was lower, another study we carried out revealed the same kind of hypersensitivity in children.¹² We also demonstrated that delayed hypersensitivity to APs is related to MHC genes.¹³

Hertl et al¹⁴ isolated CD8⁺ T-cell clones from the

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peripheral blood of patients with maculopapular eruptions caused by delayed hypersensitivity to a β -lactam (eg, ampicillin [AM] or benzylpenicillin [BP]).¹⁴ They also showed that CD8⁺ T cells predominated in lesional skin from patients with β -lactam-induced bullous reactions.¹⁵ Delayed cellular hypersensitivity in amoxicillin (AX)-induced morbilliform rashes is also indicated by immunohistologic results in biopsy specimens regarding positive patch test or delayed intradermal test responses, as well as in the initial biopsy specimens of the rashes.¹⁰

In many other cases of AP-associated maculopapular rashes, there was no evidence of immune-mediated mechanisms of any type, and challenges with the suspect APs were well tolerated.¹⁶

This study was conducted to determine the significance and incidence of skin test reactions to APs in adults reporting adverse reactions during therapy with these β -lactams and, particularly, to evaluate the contribution to the diagnosis of delayed-reading skin tests, patch tests, and challenges in a group with histories of nonimmediate cutaneous eruptions.

METHODS

We studied all the adults seen by our staff between January 1994 and December 1997 who had histories of adverse reactions to APs. All of the subjects underwent several immunoallergologic tests.

Prick and intradermal skin tests

Prick and intradermal tests were performed with the following agents. Penicilloylpolylysine (PPL) (Allergopen, Reinbeck, Germany) undiluted solution was obtained by reconstituting the lyophilized contents of a vial containing 0.175 mg PPL plus 20 mg mannitol in 5 mL of buffer. A 1:10 dilution of this solution in 0.9% NaCl was initially used. When results were negative, testing was repeated with the undiluted solution. Minor determinant mixture (MDM) (Allergopen), containing 0.6 mg BP and 0.5 mg benzylpenicilloate per milliliter initially diluted 1:10,000 in 0.9% NaCl, was also used. Tests were repeated with a 1:10 dilution when initial results were negative. Another agent used was BP (Pharmacia, Milan, Italy) diluted in 0.9% NaCl and administered at increasing concentrations ranging from 0.1 IU/mL to 10,000 IU/mL. Finally, AM (Amplital, Pharmacia) and AX (Velamox, SmithKline Beecham, Milan) were used, both at concentrations of 1 mg/mL and 20 mg/mL, after dilution in 0.9% NaCl. All haptens were initially tested on volar forearm skin by using the prick technique. Reactions were considered positive when a wheal greater than 3 mm in diameter was present 15 to 20 minutes after testing. When negative results were observed, 0.02 mL of the hapten solution was injected intradermally on volar forearm skin, and readings were made at 20 minutes and 48 hours. Results were considered positive when wheals greater than 5 mm were present. Positive controls for prick and intradermal tests were performed with histamine (10 mg/mL and 1 mg/mL, respectively); normal saline was used as a negative control. Control intradermal tests with AM and AX were also administered to 30 healthy subjects who had previously been treated with 1 or more of these penicillins without any adverse effects.

Patch tests

Patch tests were administered to all subjects who had experienced nonimmediate reactions with BP (5000 IU/g petroleum jelly), AM (5% in petroleum jelly), and AX (5% in petroleum jelly) (F.I.R.M.A., Florence, Italy). All reagents were applied to unin-

involved skin on the interscapular region of the patient's back by using acrylate adhesive strips with small plates attached for test allergens (Curatest, Lohmann GmbH and Co KG, Neuwied, Germany). Occlusion time was 48 hours. Readings were made, as recommended by Wilkinson et al,¹⁷ 15 minutes after removal of the strips and 24 hours later. Control patch tests in 30 healthy subjects who had previously tolerated 1 or more of these penicillins were also performed.

RASTs

In vitro assays for antigen-specific IgE to penicilloyl G, penicilloyl V, AM, and AX were performed by using the Phadebas RAST (Pharmacia, Uppsala, Sweden).

Challenges

Subjects with nonimmediate reactions who had negative responses to all of the above tests or displayed positive delayed intradermal test responses and negative patch test responses underwent oral challenges with the suspect penicillin (AM [Amplital] or AX [Velamox]). We administered an initial dose of 5 mg. In subjects with negative results, 1 week later we administered 50 mg and, if the result was again negative, 500 mg was added after another week. Informed consent was obtained from all subjects, who were admitted to a day hospital for 24 hours for administration of the challenge.

As explained in greater detail at the end of the Discussion section, on the basis of the results of our previous studies^{11,13} we believed it was unjustified to perform challenges that could cause suffering in patients with positive patch test and delayed intradermal test responses to the suspect drug.

Statistical analysis

The differences between means were evaluated by Student's *t* test for unpaired data.

RESULTS

We examined a total of 193 adults (142 women and 51 men), ranging in age from 13 to 74 years (mean age, 39.90 ± 16.94 years), with histories of adverse reactions to APs. Our work-up was performed 50.14 ± 79.53 months (range, 1 to 540 months) after the most recent drug administration.

AX was the causative AP in 86 patients, followed by AM in 48 and bacampicillin (BC) in 34. Twenty-five subjects had distinct reactions to different APs in separate episodes (15 to AM/AX, 5 to AX/BC, 4 to AM/BC, and 1 to AX/AM/BC). Patients had a total of 235 reactive episodes. The clinical manifestations described by the subjects are listed in Tables I and II. The most frequent were maculopapular rashes (111 subjects), followed by urticaria and urticaria-angioedema. One patient had linear IgA bullous dermatosis, a subepidermal blistering disease characterized by linear deposition of IgA along the basement membrane zone, which can be provoked by many different drugs, even in the same patient.¹⁸ Twenty-nine patients experienced anaphylactic shock, including urticaria, angioedema, or both. All anaphylactic reactions were immediate, whereas all maculopapular rashes were nonimmediate. If a patient had different kinds of immediate reactions in separate episodes, he or she was classified as being in the most severe category. All

TABLE I. Immediate manifestations and results of allergologic evaluation

Symptoms	No. of patients	No. of episodes	No. of patients with IH
Anaphylactic shock	29	32	25
Urticaria/angioedema	11	14	9
Urticaria	7	8	5
Angioedema	2	2	1
Total	49	56	40

IH, Immediate hypersensitivity diagnosed on the basis of positive skin test and/or RAST results.

TABLE II. Nonimmediate manifestations and results of allergologic evaluation

Symptoms	No. of patients	No. of episodes	No. of patients with DH
Maculopapular rash	111	146	61
Urticaria	12	12	—
Erythema	8	8	1
Urticaria/angioedema	5	5	—
Angioedema	5	5	—
Anaphylactoid purpura	2	2	—
Linear IgA bullous dermatosis	1	1	—
Total	144	179	62

DH, Delayed hypersensitivity diagnosed on the basis of positive patch test and/or delayed intradermal test responses and oral challenge responses.

patients reporting maculopapular rashes were classified as being in the maculopapular category whether or not they also presented angioedema, skin scaling, or both.

Skin tests and/or RASTs indicated that 40 of the 49 (81.63%) subjects with immediate manifestations had experienced type-I hypersensitivity reactions (Table I). Of the 37 subjects with positive skin test responses, 9 reacted only to APs and 6 only to penicillin determinants, whereas the others reacted to both (Table III). The remaining 3 had positive RAST results and negative skin test responses.

Among subjects who had experienced nonimmediate cutaneous manifestations, none was given a diagnosis of an IgE-mediated hypersensitivity reaction.

Fifty-eight subjects had positive patch test and delayed intradermal test responses to AM and AX, which, on the basis of our previous studies,^{11,13} was considered indicative of delayed hypersensitivity.

Positive patch test and delayed intradermal test responses to AM and AX constituted the main pattern of reactivity, followed by positive patch test and delayed intradermal test responses to BP, AM, and AX (Table IV). The 5 subjects with positive delayed intradermal test responses to BP, AM, and AX and positive patch test responses only to AM and AX reacted to the highest concentration of BP. The maximum diameters of positive delayed intradermal test responses (indurated erythematous lesions) at an AP concentration of 20 mg/mL ranged

TABLE III. Patterns of skin test reactivity in 37 of 40 patients with immediate hypersensitivity to APs

PPL	MDM	BP	AM	AX	No. of patients
—	—	—	+	+	6
—	—	—	+	—	2
—	—	—	—	+	1
+	—	—	—	—	2
—	—	+	—	—	2
+	+	+	—	—	1
—	+	+	—	—	1
—	+	+	+	+	11
+	+	+	+	+	3
—	—	+	+	+	2
—	—	+	+	—	2
+	+	+	+	—	1
—	+	—	+	+	1
+	—	+	+	—	1
+	—	—	+	+	1

TABLE IV. Patterns of skin test and patch test reactivity in 62 patients with delayed hypersensitivity to APs

Intradermal test delayed response				Patch test response			No. of patients
MDM	BP	AM	AX	BP	AM	AX	
—	—	+	+	—	+	+	42
—	+	+	+	+	+	+	8
—	+	+	+	—	+	+	5
+	+	+	+	+	+	+	3
—	—	+	+	—	—	—	3*
—	+	+	+	—	—	—	1†

*Two subjects with oral challenge confirmation and 1 unchallenged subject because of ulcerative rectocolitis.

†Unchallenged because of slight maculopapular rash 12 hours after intracutaneous tests.

from 9 to 60 mm, with more than 70% exceeding 20 mm, whereas at an AP concentration of 1 mg/mL diameters ranged from 6 to 26 mm, with more than 50% exceeding 10 mm. All of the patients with delayed reactions to intradermal skin tests reacted to both the 1-mg and 20-mg concentrations.

Positive patch test responses were as follows: AM⁺/AX⁺ in 37 subjects (BP⁺ in 3); AM⁺⁺/AX⁺⁺ in 15 (BP⁺ in 4 and BP⁺⁺ in 3); AM⁺⁺⁺/AX⁺⁺⁺ in 2 (BP⁺⁺ in 1); AM⁺/AX⁺⁺ in 3; and AM⁺⁺/AX⁺ in 1.

Of the 79 patients who had experienced nonimmediate reactions (49 with maculopapular rashes and 30 with nonmaculopapular manifestations) and had negative results on allergologic testing (both immediate and delayed-type skin tests and RASTs), 64 agreed to submit to challenges with the suspect penicillin (AX in 40 and AM in 24). None of the 42 patients with maculopapular rashes reacted to the suspect drug, whereas in the group of 22 subjects with nonmaculopapular manifestations, the only subjects who reacted (to AX) had linear IgA bullous dermatosis.

Of the 4 patients who had maculopapular eruptions

during AP therapy and who had positive delayed intradermal test responses and negative patch test responses, 1 tolerated the suspect AP, 1 reacted to the challenge, and the other 2 were not challenged because of ulcerative rectocolitis and a slight maculopapular rash that appeared 12 hours after intracutaneous tests, respectively. The last 3 subjects were considered as having had delayed hypersensitivity reactions, the one with ulcerative rectocolitis because she had experienced 2 distinct reactions to AM and AX in separate episodes that had persisted for about 2 weeks after the antibiotic had been withdrawn and steroid treatment started.

All 3 patients with AP-induced nonmaculopapular eruptions who had positive delayed intradermal test responses and negative patch test responses received oral challenges. Of the 2 subjects who had erythematous rashes, one reacted positively 5 hours after AX administration (5 mg), with the same eruption as before, and the other tolerated AM. The third subject, who had recurrent urticaria and had experienced an urticarial rash on the third day of AX therapy, did not react to the challenge; laboratory tests detected 760 IU/mL of antibodies against the hepatitis B surface antigen (HBsAg). Overall, we found 62 patients with delayed hypersensitivity to APs.

The mean time of rash resolution was longer in the delayed hypersensitivity group (14.05 ± 9.94 days) than in the group with negative results in allergologic evaluations, including challenges (5.43 ± 3.56 days). This difference is statistically significant ($t = 5.829$; $P < .001$). In addition, the percentage of patients who experienced more than 1 episode was higher in the group with cell-mediated hypersensitivity than in the group with negative results in allergologic work-ups (44.26% vs 8%). The former also displayed angioedema, skin scaling, or both more frequently (57.60% of 92 episodes vs 14.81% of 54 episodes).

The mean time interval between the most recent reaction and our tests was significantly longer ($t = -2.774$; $P < .01$) in the delayed-type (71.81 ± 104 months) than in the IgE-mediated type responses (24.0 ± 39.01 months).

DISCUSSION

Our study indicates that patch tests and delayed-reading intradermal tests are necessary tools in evaluating nonimmediate reactions to APs, particularly morbilliform rashes. In effect, of the 119 subjects with erythematous or maculopapular rashes, 62 displayed delayed hypersensitivity (Table II), and 45 of the latter (72.6%) reacted only to AM and AX (Table IV). Therefore in patients reporting nonimmediate reactions to APs it is important to perform skin tests with these β -lactams in addition to penicillin determinants (PPL, BP, and MDM).

Other researchers have reported similar results in studies of patients with nonimmediate reactions to APs,^{4,8,10} confirming the importance of side-chain determinants in such patients, as demonstrated by Voorhost and Sparreboom.¹⁹ The amino side-chain seems less important in IgE-mediated reactions: only 9 of our 40 subjects

(22.5%) with immediate hypersensitivity had positive skin test responses for APs alone (Table III). In any case, in diagnosing immediate reactions to APs, one should use these drugs for testing.

Positive patch test responses in the evaluation of nonimmediate reactions have a diagnostic value similar to that of the tuberculin-like reactions appearing 12 to 24 hours after intradermal injections of APs.

Intradermal testing appears to be more sensitive than patch testing because there are subjects with delayed reactions who have negative patch test responses and positive delayed intradermal test responses. The reasons for this phenomenon are not clear, but it may be connected with the fact that the haptens are processed in different parts of the skin. In any case this pattern of skin reactivity needs further investigation because of the existence of false-positive cases. RASTs did not prove to be useful in evaluating nonimmediate reactions because no positive results were found among patients reporting such reactions.

Both this study and previous studies we carried out on adults,¹¹ as well as children,¹² indicate that delayed hypersensitivity to APs is a long-lasting condition that does not appear to be influenced by the time interval between the last adverse reaction and allergologic testing. Therefore it is unlikely that subjects who had experienced delayed hypersensitivity reactions and had negative allergologic results would have lost their hypersensitivity. Although more extensive and detailed studies would be useful, negative results in patch and intradermal tests with an appropriate panel appear to be a fairly reliable indicator that the cutaneous eruptions are not allergic reactions to APs but rather manifestations of the infectious disease. In addition to those associated with the classic childhood exanthems, a number of other viruses that provoke nonspecific upper respiratory tract symptoms can produce morbilliform rashes.²⁰ These cutaneous eruptions may also result from interaction between viruses and antibiotics, as in infectious mononucleosis.²¹

In this study all 42 subjects who reported the eruption of exanthems during AP therapy and had negative results to allergologic tests responded negatively to challenges with the suspect antibiotic, confirming the indication of our previous studies that negative results in allergologic tests seem to exclude the allergic nature of maculopapular rashes.^{11,12}

All patients with nonimmediate urticarial and/or angioedematous reactions who had negative skin test and RAST results and agreed to undergo challenges tolerated the suspect penicillin.

Drug-associated urticaria is usually interpreted as a manifestation of allergy, but during acute febrile illness it may be caused by the infectious organism itself (eg, EBV, several Coxsackie viruses, Echovirus 11, mumps virus, hepatitis B virus, and *Mycoplasma pneumoniae*).^{20,22}

Although the results of our study seem to exclude such a possibility, nonimmediate urticarial and/or angioede-

matous manifestations occurring less than 3 hours after drug administration might be IgE mediated. Therefore negative skin test results in patients with such manifestations should be interpreted in light of the time that has elapsed since their last exposure to the drug. In fact, there are indications that in cases of IgE-mediated allergy, skin tests are more likely to be positive the less time has elapsed since the clinical reaction.²³⁻²⁶ In a study of 42 children with IgE-mediated hypersensitivity to penicillins, Chandra et al²⁵ reported that skin test responses became negative in one third of those who had positive reactions a year earlier.

In this study 9 of the 33 subjects (27.27%) who had experienced nonmaculopapular nonimmediate reactions were tested more than a year after their most recent reaction and had negative skin test and RAST results, which was confirmed in the 6 who agreed to undergo challenges. In any case, it is advisable to retest such patients after 4 weeks or more, as in the study by Mendelson et al,²⁷ to exclude a possible resensitization after loss of sensitivity, particularly in those who reacted less than 3 hours after drug administration.

Our testing protocol allowed us to clarify the nature of the nonimmediate manifestations experienced by 129 (89.58%) of the 144 patients studied. Delayed hypersensitivity was confirmed in 43.05% (62 of 144), whereas in 45.83% (66 of 144) negative reactions to challenges allowed us to reasonably exclude the possibility of allergy; 1 patient had linear IgA bullous dermatosis, which was confirmed by challenge. Definitive diagnoses could not be provided for the remaining 10.42% (15 of 144) who had negative allergologic test results because they did not consent to undergo challenges.

In conclusion, penicillin-associated nonimmediate skin rashes are very common in adults. Our diagnostic protocol can be helpful in clarifying the nature of many of these reactions. A large percentage of AP-induced maculopapular rashes involves a delayed hypersensitivity mechanism, which is indicated by both positive patch test and delayed intradermal test responses. This pattern of positivity does not need to be supported by challenges because in our previous studies^{11,13,28} all such patients reacted, often severely, when provoked with the culprit drug.

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