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Diagnosis of Immediate Hypersensitivity to β-Lactam Antibiotics Can Be Made Safely with Current Approaches

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Key Words
Allergy · β-Lactams · Hypersensitivity · Penicillin · Skin tests

Abstract
Background: Diagnosing immediate hypersensitivity to β-lactam antibiotics is still a significant problem. Recently, a new penicillin testing reagent was introduced to the market. In this study, the recommendations of the European Network of Drug Allergy (ENDA) for the diagnosis of immediate reactions to β-lactams were followed, and the negative predictive value of this approach with currently available reagents was assessed. ***Methods:*** Eighty patients (age range: 6–74 years) with a history of immediate reactions to β-lactams were included. All cases underwent skin testing with benzylpenicilloyl-polylysine (PPL) and minor determinant mixture (MDM), followed by the culprit drug if necessary. If this step was negative, a drug provocation test was offered. If this step also yielded a negative result, then the patients were recommended to use β-lactam antibiotics in future whenever their use was indicated. ***Results:*** Overall, 29 patients (36.2%) were diagnosed as β-lactam allergic. The majority of the cases (72.4%) were diagnosed by positive skin tests to either PPL or MDM, whereas 10.3% were diagnosed by skin testing with culprit drugs and 17.2% with drug provocation tests. Regarding the use of the tested drug in the long term, almost half of the contacted patients had had an indication to use the tested drug and the majority had taken the whole course without problems. ***Conclusions:*** Although currently available new penicillin tests provide sufficient allergy data, all the steps recommended by ENDA should be followed in the diagnosis of immediate reactions to β-lactams. If these steps are negative, the patients usually tolerate β-lactams and only a few develop mild, non-life-threatening reactions in the long term.

Introduction

Hypersensitivity reactions to β-lactam antibiotics are among the most common drug reactions [1–3]. Since their introduction to the market, penicillin skin tests with major (benzylpenicilloyl-polylysine, PPL) and minor determinants (minor determinant mixture, MDM) of penicillin have had a major impact on the diagnosis of immediate hypersensitivity to β-lactams [1, 2]. Application of these tests in clinical practice has revealed that the majority of patients with a history of immediate reactions

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to β-lactams were not really allergic to penicillin [4, 5]. However, in 2004, the whole world was faced with a serious problem of withdrawal of penicillin skin tests from the market. Indeed, this absence caused many problems in managing patients with a history of β-lactam allergy and eventually led many physicians to prescribe more toxic and expensive broad-spectrum antibiotics. During this period, the European Network of Drug Allergy (ENDA) emphasized the importance of these reagents in diagnosing immediate reactions to β-lactams [6–8]. Finally, a Spanish company developed new penicillin skin testing reagents with major and minor determinants of penicillin. Afterwards, a few studies performed in a limited number of cases showed encouraging results with these tests [9–12]. However, further investigations of the diagnostic value of these tests in more patients are still needed.

Recent studies indicated a different sensitization profile in patients with β-lactam allergy with replacement of benzylpenicillin (BP) mainly by amoxicillin which could not be detected by testing with PPL and MDM alone [13–17]. As a result of this, ENDA recommended the use of skin testing not only with PPL and MDM but also with culprit drugs in order to detect side chain-specific allergies [18, 19]. If all skin tests are negative, drug provocation tests as a final evaluation are also advisable. However, limited data are available regarding the predictive value of this approach with currently available reagents for safety in the long term.

In this study, a group of patients including both children and adults with a history of immediate reactions to β-lactam antibiotics were tested according to the recommendations of ENDA in order to document the rate of true β-lactam allergy. The cases with an overall negative allergy workup for β-lactam allergy were also evaluated with regard to the consequences of long-term use of β-lactam antibiotics.

Material and Methods

Study Group

This study included 80 patients with a history of immediate reactions to β-lactam antibiotics who were admitted to the Departments of Adult and Pediatric Immunology and Allergy of a university hospital between 1 March 2008 and 31 November 2009. Patients who had experienced severe reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, drug-induced hypersensitivity reactions and acute generalized exanthematous pustulosis as well as clinical manifestations of specific organ involvement and a history of anaphylactic shock in the preceding year were not included. Tests were not performed in patients who had had an immediate reaction within the last 4–6 weeks, used medication which could affect the test outcome such as antihistamines or had active signs of an underlying disease such as urticaria, uncontrolled asthma and uncontrolled cardiac diseases.

Diagnosis of β-Lactam Allergy

In this evaluation, the recommendations of ENDA were followed. Written informed consent was obtained from the patients prior to the study. The local ethics committee approved the study.

Skin Tests

Skin tests were performed under strict medical supervision. On the first day, all patients were tested with penicillin major determinants (PPL) and minor determinants (MDM; Diater, Madrid, Spain). If the results of PPL and MDM testing were negative, the patients were tested with the culprit drug if one existed in their history. The concentrations of culprit drugs were mainly selected on the basis of nonirritating doses reported in the previous literature [18, 19].

Testing was performed according to the recommendations of the manufacturer in an escalating algorithm as follows: firstly a prick test with undiluted PPL, then intradermal tests with a 1:10 dilution and finally an undiluted sample. MDM was tested correspondingly. In cases with suspicion of high sensitivity, initially a more diluted concentration was used. In addition to drugs, the tests included negative (serum physiologic) and positive (histamine) controls as well. The skin tests were considered positive if a wheal diameter was 3 mm greater than the negative control and accompanied by erythema after 15–20 min.

Late readings of an intradermal test at 48, 72 and 96 h were performed in those patients in whom urticaria developed within 2 h of the use of any β-lactam or with unknown timing. Patch tests were performed with 10 and 30% concentrations of the culprit drugs in white petrolatum. The readings were made based on the recommendations of the European Society of Contact Dermatitis.

Drug Provocation Tests

A single-blind, placebo-controlled drug provocation test was performed in the patients with negative skin tests. Amoxicillin was the drug of choice as it is one of the most commonly prescribed β-lactam antibiotics in our country. However, in some cases, tests were also carried out with culprit drugs. Both placebo and active drug were given at similar doses and intervals on separate days. As an example, doses of amoxicillin were 5, 50, 150, 250 and 500 mg, which were given within 1-hour intervals. On the day of testing, values of initial baseline blood pressure and forced expiratory volume in 1 s (FEV_1) were recorded. During the challenge procedure, blood pressure and FEV_1 values, as well as skin, ocular, nasal and bronchial reactions, were monitored every hour after each placebo or active drug dose was given. The patients were kept under strict medical observation for up to 2 h after completing the test in the case of a negative test. The tests were considered negative if no adverse reaction occurred at the end of 24 h. Tests were considered positive if any sign of hypersensitivity reactions such as urticaria, angioedema, laryngeal edema, hypotension, dyspnea, nasal symptoms, 20% fall in FEV_1 value, anaphylaxis or other rashes were observed during or after the test. In the case of a positive reaction, the tests were stopped and the patients were treated according to their symptoms and were kept under medical observation until all symptoms were completely resolved.

Statistics

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 11.0 (SPSS, Chicago, Ill., USA). Numeric values were expressed as means ± SEM whereas nominal values were given as numbers and percentages. Assessments of risk factors for developing positive reactions to β-lactams were performed by univariate analysis. The factors in this analysis were age, gender, duration of drug allergy, presence of asthma, chronic urticaria, atopy, other drug hypersensitivity, type of previous reactions and culprit drugs. All directional p values were two-tailed, and significance was assigned to values lower than 0.05.

Results

Clinical Manifestations and Culprit Drugs

The study included 80 cases (66 females, 14 males; mean age 35.2 ± 1.7 years; table 1). The majority of the cases (42; 53.8%) had urticaria as the clinical manifestation of β-lactam allergy. The most common culprit drugs were penicillin G and V, in half of the cases (40; 50%), whereas amoxicillin and the second-generation cephalosporins represented the other most commonly involved β-lactams (table 1). The time that had elapsed since the last reaction was 148 ± 20.4, 32.4 ± 8.1 and 23.3 ± 6.2 months, respectively, for patients allergic to penicillin G/V, amoxicillin and cephalosporins.

Table 1. Demographics and disease characteristics of the patients with β-lactam hypersensitivity

Variable	
Number	80
Females, n	66 (82.5)
Age, years[1]	35.2 ± 1.7 (6–74)
Time since the last reaction, months[1]	96.8 ± 12.5 (1–480)
Culprit β-lactam in history, n	
Penicillin G and/or V	40 (50)
Amoxicillin	24 (30)
Ampicillin	13 (16.2)
Cephalosporin 1st generation	1 (0.01)
Cephalosporin 2nd generation	16 (20)
Cephalosporin 3rd generation	3 (0.03)
Other β-lactam antibiotics	5 (0.06)
Allergic manifestation, n	
Urticaria	42 (53.8)
Anaphylaxis	23 (29.1)
Anaphylactic shock	4 (5.1)
Dyspnea	4 (5.1)
Others	7 (8.7)
Presence of atopy, n	17 (32)
Comorbidities, n	
Asthma	26 (32.5)
History of drug hypersensitivity to drugs other than β-lactam antibiotics	34 (43.6)
Chronic urticaria	11 (13.8)

Figures in parentheses represent percentages, except where indicated otherwise.

[1] Mean ± SEM with range in parentheses.

Results of Workup for β-Lactam Antibiotic Allergy

Overall, among 80 cases with a history of immediate-type reactions to any β-lactam antibiotics, 29 (36.2%) were diagnosed as β-lactam allergic based on test results. Among the positive cases, 21 (72.4%) had positive skin prick/intradermal tests to penicillin determinants (PPL and MDM; fig. 1; table 2), while 3 (10.3%) showed positive skin test results to culprit drugs (cefuroxime in 2 cases, cefixime in a single case). Among the 56 cases with negative skin tests, 40 agreed to undergo drug provocation tests. Five patients (17.2%) developed positive reactions to drug provocation tests (table 2). Four patients underwent delayed reading of intradermal and patch tests. All were negative. The skin tests usually provided safe conditions for patients. Four cases had reactions such as cough with sore throat. All reactions occurred during the tests with penicillin minor determinants. These reactions quickly responded to medical treatment.

The time that had elapsed since the last reaction was significantly shorter in patients with a positive allergy workup for β-lactams than those with a negative allergy workup. The class of culprit β-lactam antibiotic in the patient's history, gender, age, type of previous reaction, presence of comorbidities such as asthma, rhinitis and chronic urticaria, history of drug hypersensitivity to other drugs and atopy did not influence the positive results.

Long-Term Use and Safety

Among the 51 cases who had a negative allergy workup for β-lactam hypersensitivity, 32 were able to be contacted by phone at least 12 months after the negative test. Fourteen of them reported to have had an indication to use the tested drug. Twelve cases used a whole course of the drug without any problem. One case had had mild urticaria that developed 4 h after the 5th dose of the drug. Another patient with a negative test did not agree to use the tested drug and preferred to use an alternative agent recommended by a physician. On the other hand, among the 18 cases who reported to have had no indication to use the tested drug, 4 reported that they would prefer not

Table 2. Characteristics of the patients with a positive allergy workup for immediate-type β-lactam antibiotic allergy

Age years	Gender	Culprit β-lactam antibiotic	Other culprit β-lactam antibiotics	Time since the last reaction months	Previous reaction in history	Positive reaction on skin prick test/ intradermal test to	Positive reaction to	Test drug for DPT	Results of DPT
NR	female	pen G and V		60	urticaria	minor determinant	direct ID		not performed
58	female	ampicillin	cephalosporin 2nd generation	12	urticaria	major determinant	1/10 ID		not performed
30	female	amoxicillin	cephalosporin 2nd generation	48	anaphylaxis	minor determinant	1/10 ID		not performed
44	female	pen G and V		24	anaphylaxis	minor determinant	1/10 ID		not performed
36	female	pen G and V		84	urticaria	major determinant	1/10 ID		not performed
9	female	pen G and V	ampicillin	72	urticaria	major determinant	direct ID		not performed
52	female	pen G and V		84	urticaria	major determinant	direct ID		not performed
23	female	pen G and V	ampicillin	24	anaphylaxis	minor determinant	1/100 ID		not performed
52	female	amoxicillin		1	urticaria	major determinant	direct ID		not performed
49	female	cephalosporin 2nd generation	cephalosporin 2nd generation	24	urticaria	minor determinant	1/100 ID		not performed
30	female	not known		12	urticaria	minor determinant			not performed
26	female	amoxicillin		12	anaphylaxis	negative		amoxicillin	positive
42	female	pen G and V		NR	urticaria	major determinant	direct ID		not performed
33	female	cephalosporin 1st generation		36	anaphylactic shock	minor determinant	direct ID		not performed
13	female	ampicillin	pen G and V	120	anaphylaxis	major determinant	1/10 ID		not performed
19	female	pen G and V		48	pruritis and erythema	negative		amoxicillin	positive
10	female	cephalosporin 3rd generation	pen G and V	18	anaphylaxis	cefixime			not performed
56	female	pen G and V		NR	anaphylactic shock	minor determinant	1/1,000		not performed
49	female	pen G and V		120	anaphylaxis	minor determinant	1/1,000		not performed
11	male	pen G and V		9	anaphylaxis	major determinant	1/10 ID		not performed
22	male	pen G and V		108	anaphylaxis	minor determinant	1/10 ID		not performed
41	female	cephalosporin 2nd generation	cephalosporin 2nd generation	60	anaphylactic shock	cefuroxime			not performed
33	female	amoxicillin		2	urticaria	major determinant	direct ID		not performed
33	female	cephalosporin 2nd generation		60	anaphylaxis	cefuroxime			not performed
29	female	pen G and V		1	urticaria	minor determinant	1/10 ID		not performed
43	female	amoxicillin		48	urticaria	systemic reactions		amoxicillin	negative
47	female	pen G and V	ampicillin	240	dyspnea	negative		ampicillin	positive
35	female	cephalosporin 2nd generation		18	anaphylaxis	negative		amoxicillin	positive
45	female	cephalosporin 2nd generation	cephalosporin 2nd generation	9	urticaria	negative		amoxicillin	positive

NR = Not reported; ID = intradermal; DPT = drug provocation test.

to use these tested drugs in future even if an indication occurs as they still have significant fears despite a negative allergy workup for β-lactam allergy. These findings are summarized in figure 2.

Discussion

Similar to previous findings, this study showed that the actual rate of β-lactam-allergic patients was low in patients describing a history of immediate reactions to β-lactams. Our results confirmed a good diagnostic value of currently available new penicillin skin tests of major and minor determinants to detect many of the cases with immediate hypersensitivity to β-lactam antibiotics in a group which included both children and adult patients who were mainly allergic to penicillin G and/or V. Our results also indicated the requirement of inclusion of skin testing with culprit drug(s) in particular in cases with negative penicillin skin testing as there are patients who react to the side chain of the relevant drugs. Overall, negative allergy workup for β-lactam allergy including final

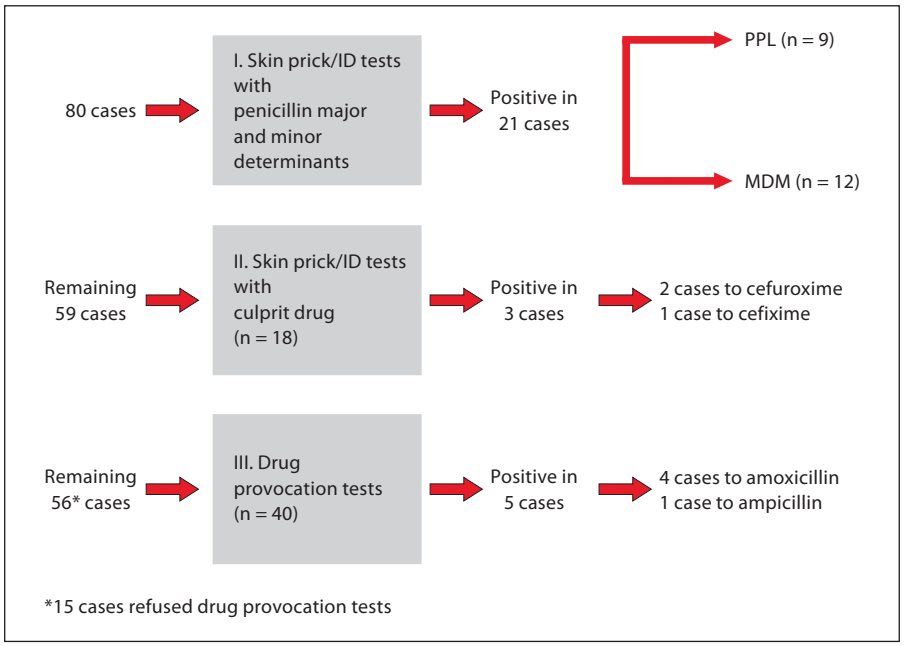

Fig. 1. Schematic view of algorithmic evaluation of immediate hypersensitivity to β-lactam antibiotics. ID = Intradermal.

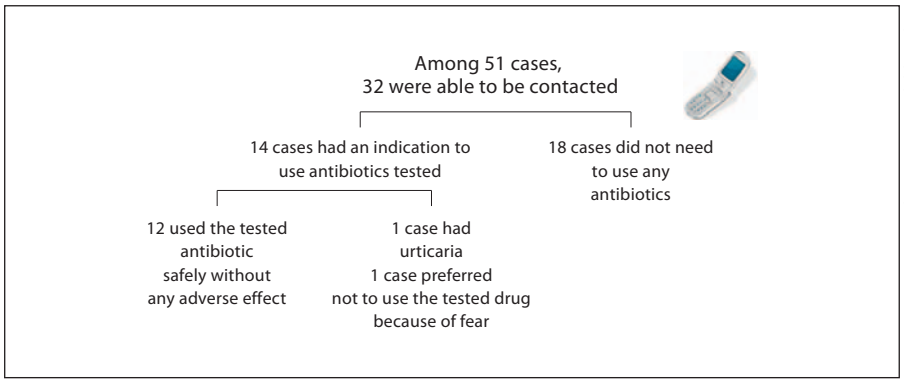

Fig. 2. Long-term use of β-lactam antibiotics among patients with a negative allergy workup for β-lactam hypersensitivity.

evaluation with drug provocation tests in the case of negative skin tests indicated a high negative predictive value (NPV) of this approach for determining the safe use of these drugs in future.

Earlier studies suggested that if skin testing with PPL and MDM was negative, only 1% of patients would have reacted to oral penicillin, which gives an NPV of 99% [4, 5]. However, these results belonged to the data from earlier patient series, when narrow-spectrum penicillins, usually penicillin V and G, were commonly prescribed. In recent decades, a shift in the preference of β-lactam prescriptions towards broad-spectrum penicillins has been observed in many countries [20]. As a result of this, recent studies have shown a different pattern of IgE sensitization from that of previous studies. These studies indicated that a significant proportion of allergic patients produced amoxicillin-specific IgE, which was likely related to the high use of broad-spectrum penicillins in southern Europe [13, 14, 17].

Antibodies against the amino side chain of amoxicillin or other β-lactams could not be identified by testing with PPL or MDM. In a Spanish study of 203 patients with positive skin tests to penicillin by Torres et al. [21], 43% were positive to amoxicillin alone and 55% to PPL or MDM. In line with these data, a study from France by Bousquet et al. [22] showed that among cases with negative skin tests to PPL or MDM, 17.4% had a positive skin response to the culprit drug, indicating the requirement of additional steps to diagnose true β-lactam allergy. Moreover, 30.7% of the cases were diagnosed by drug

challenge tests. This group determined that the NPV for PPL/MDM reagents was only 85.1%, which was lower than that of 99% provided by earlier studies. Our results also confirmed these data. In our study group, the majority of the cases with documented β-lactam allergy were diagnosed by positive skin tests to either PPL or MDM, while 10.3% were diagnosed by skin testing with culprit drugs and 17.2% by drug challenge tests. As the predominant antibiotic to which our study population was allergic was penicillin G and/or V, this could explain the higher positivity rates to PPL and MDM in accordance with earlier studies. However, the change in the preferential β-lactams prescribed in our country is reflected in our findings and, similar to southern Europe, amoxicillin was the second most common drug responsible for allergy in our series. In line with this, and owing to the presence of cases with side chain-specific allergy, the NPV of PPL and MDM (80%) in our group was not as high as previously reported. So, assuming the changes in β-lactam prescription and allergy profiles, our data once again support the recommendations to perform skin tests with culprit drugs and drug challenge tests as final evaluations in patients with a history of immediate allergy to β-lactams.

With regard to the safety issues of penicillin skin testing, 8% of a large series of 147 skin test-positive patients were reported to experience a systemic reaction induced by previous testing materials [23]. However, limited data exist about the safety of new tests. So far, other than a single case from Australia [11], no significant systemic reaction with the new reagents has been reported. Application of 4 different reagents to the patients at the same time could very likely be the reason for the severe reaction in that particular case [11]. In our study group, only 4 patients developed mild systemic reactions, all of which resolved completely after adequate treatment. None of the pediatric patients developed adverse reactions. Thus, our data suggest the safety of these tests in children as well.

The time that had elapsed since the previous reaction was the only factor to predict a positive test to β-lactams. The cases with a negative workup had a longer time interval (>10 years) since the last reaction. Contrary to this, all of the positive cases had had their last reaction to β-lactams within the previous 10 years. Moreover, these reactions had occurred within the previous 5 years in 24 out of 29 patients. Thus, it can be assumed that the patients with a history of a β-lactam allergy within the previous 5 years have a higher likelihood of having a positive reaction to these tests.

In our series, among 80 cases, 51 were considered non-allergic to β-lactam antibiotics. These patients were recommended to use the tested β-lactams in future in the case of a proven indication. Among 32 patients who could be reached by phone at least 12 months after testing, almost half had had an indication to use the tested drugs and the majority tolerated the whole treatment course without any adverse effect. In the largest documentation so far in southern Europe, the NPV of the evaluations recommended by ENDA was found to be very good (94.7%) with regard to long-term use [24]. Despite the limited number of cases, our results suggest that the evaluations recommended by ENDA predict the safe use of the drug in the long term. However, interestingly, 5 cases reported that they would prefer not to use these drugs in future even if an indication occurs as they still have significant fears despite a negative allergy workup for β-lactam allergy. Actually, this fear described by the patients is an important issue that allergists must consider when discharging patients with a negative allergy workup for β-lactam allergy.

In this study, we did not analyze specific IgE to penicillin in our group. However, although previous trials suggested a moderate sensitivity for the diagnosis of immediate reactions to β-lactams, recent studies have failed to show such a diagnostic use in patients with remote histories of penicillin allergy [25–28].

In our study, the rate of patients with urticaria who underwent patch tests and delayed reading of intradermal tests was low, mainly due to the poor compliance of patients with these tests. So, although we cannot declare any diagnostic value of these tests in our group, recent data indicate a poor diagnostic value of these tests for no immediate reactions [29]. In this study, we did not perform BP testing. However, the diagnostic contribution of BP testing in patients with immediate reactions to β-lactams over a negative MDM/PPL test was reported to be very small [30]. BP testing is strongly recommended in the absence of MDM/PPL skin tests in clinical practice. Moreover, we performed drug provocation tests in skin test-negative patients. So, we may assume that we did not miss any patient with β-lactam allergy despite not performing BP testing in PPL/MDM-negative cases.

In conclusion, our results confirmed the requirement of testing of patients with β-lactam hypersensitivity with currently available penicillin kits as well as skin testing with culprit drugs and drug provocation tests if necessary. After all these steps, if the tests are negative, the patients usually tolerate the use of β-lactams in future and only a few develop mild, non-life-threatening reactions.

So, this finding might encourage physicians to prescribe β-lactams. Considering patients' fears about this allergy, allergists should spend more time educating patients about the long-term significance of negative tests in order to overcome the potential fears of the patients.

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