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Original Research

β-Lactam Allergy in Children

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Abstract

Objective: β-lactam antibiotic allergy is the most common drug allergy in children. Most of the patients with suspected reactions to β-lactam antibiotics can actually tolerate these drugs. The aim of this study is to evaluate clinical and laboratory characteristics of children with β-lactam allergy and to determine cross-reactivity between penicillin and cephalosporins.

Methods: The diagnosis of β-lactam allergy was made based on the results of skin tests and/or drug provocation tests (DPT). Penicillin allergy skin tests were performed with DAP penicillin® (Diater laboratories, Madrid, Spain), penicillin G, and ampicillin/amoxicillin preparations. Skin and provocation tests were performed with the culprit cephalosporin in addition to the penicillin skin and/or provocation tests to evaluate cephalosporin allergy.

Results: We found that 87.7% (71/81) of patients with β-lactam allergy were able to tolerate the culprit drug. Among ten patients with confirmed diagnosis, two had cross-reactivity (penicillin and cephalosporin) and 8 had a various β-lactam (aminopenicillin *n*=6, ceftriaxone *n*=2) allergies. We identified older age and early-type clinical reactions as risk factors for a confirmed β-lactam allergy.

Conclusion: Skin tests and DPT appear to be useful procedures in the diagnosis, and determination of an alternative safe antibiotic in patients with β-lactam allergy. Most of the patients tolerated the drugs. A minority of the patients with confirmed allergy should avoid all β-lactam antibiotics due to the probability of cross-reactivity.

Keywords: Beta-lactams; cross-reactions; drug allergy; skin tests.

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Introduction

β-lactams antibiotics are the most common drugs that cause allergic reactions in children.[1,2] The two most frequently used members of this group are penicillins and cephalosporins.[2] The basic structure of all β-lactams is a 4-membered β-lactam ring. In addition, penicillins' have a 5-member thiazolidine ring and side chain (R), while cephalosporins have a 6-membered sulfur-containing dihydrothiazine ring and two side chains (R_1 and R_2). Theoretically, all these structures may show antigenic properties. Therefore, there is a risk of cross-reaction due to the similarity between these groups. If there is a confirmed drug allergy, the responsible drug and cross-reactive drugs should be avoided.[1-4]

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The frequency of patients suspected of penicillin allergy varies by population, about 5–15%, these patients generally avoid the all β-lactam group. With allergic evaluation, 90–98% of these patients can tolerate penicillin group drugs and almost all of them tolerate other β-lactam antibiotics.[5-7] Cephalosporin allergy is reported around 1–2% and the confirmation rate of cephalosporin allergy is much lower than penicillins.[5] Cross-reaction between penicillin and cephalosporins varies in a very wide range (0–38%) depending on the antigenic structure causing the sensitization and the similarity between the two drugs.[6-10]

In case of suspicious reactions to drugs in the β-lactam group, the whole group is generally avoided due to concerns about cross-reactions, and alternative non-β-lactam antibiotics are used in the treatment of the patient. This attitude leads to more negative consequences such as treatment failure, side effects, and nosocomial infections.[5,11] At this point, accurate diagnosis and classification of the reaction are essential in determining the next approach to patient management.

In this study, our aim was to evaluate clinical and laboratory characteristics and possible risk factors of children with β-lactam allergy and to determine cross-reactivity between penicillin and cephalosporins. We also have tested patients with confirmed allergy for cefuroxime with the purpose to find a safe antibiotic.

Materials and Methods

Patient Group

Patients who were consecutively admitted to Erzurum Regional Training and Research Hospital, Pediatric Allergy Unit between June 2012 and June 2014 with suspected β-lactam allergy were included in the study. Patient data were collected using an inquiry form based on the European Network of Drug Allergy (ENDA) drug-allergy questionnaire.[12] Informed consent was obtained from the patients and/or their families in the study.

Reactions occurring within one hour were accepted as immediate type and later ones as delayed-type.[1,3] Early readings of skin prick tests and intradermal tests (IDT) were performed in patients with immediate reactions. In patients with delayed reactions, in addition to early reading, late readings of IDT were performed on the 1st and 3rd days.[1,3,4,13] The diagnosis of anaphylaxis was made according to clinical criteria.[14]

Patients whose skin tests and/or provocation tests could not be performed due to reasons such as uncontrolled asthma, suspected serious cutaneous reaction, and family refusal was excluded from the study. The study protocol (No: 2013/70) was approved by the Ethics Committee of the same hospital and was conducted in accordance with the Helsinki declaration.

Drug Skin Tests

Tests were performed at the earliest 4 weeks after suspected reaction.[3,13] Before the tests were carried out, drugs that could affect the results were discontinued in an appropriate time. This period was not taken into account in the positivity of the penicillin test performed with benzathine penicillin preparation before injection. The tests were done with 1-week intervals, first penicillin and then cephalosporin. A bleb associated with surrounding erythema, ≥3 mm in the prick tests and, ≥5 mm in IDT or ≥3 mm compared to negative control, was considered a positive response.[13] It was started at a concentration of 1:100 in patients with initial presentation of anaphylaxis, maximum non-irritant concentration was reached in gradual increments in three applications. In delayed-type reactions, skin test was evaluated after 24th, 72nd hours, and on 7th day, repeatedly. Histamine at 10 mg/mL concentrations was used as positive and 0.9% NaCl was used as negative controls.

Penicillin tests with DAP penicillin® (Diater laboratories, Madrid, Spain), benzyl penicillin (Penicillin G, Kristasil® 50.000U vial), amoxicillin (Largopen ® 500 mg vial) or ampicillin (Ampicina® 250 mg vial) was done to all patients, respectively. Skin tests with cephalosporins were performed with cefuroxime (Zinnat® 750 mg vial) and/or ceftriaxone (Novasef® 0.5 g) considering the culprit drug in the history. Testing with cefuroxime was also performed to evaluate the cross-reaction between cephalosporins and penicillin in patients with sensitivity to skin testing with a penicillin reagent. The drug concentrations used are shown in Table 1.

Table 1. Drug concentrations used in tests†

DAP® Penicillin	0.04/0.5
Benzylpenicilloyl octa-L-lysine 0.04	1:1000–1:1 dilution
Sodium benzylpenilloate 0.5 mg	1:1000–1:1 dilution
Penicillin G	10,000 units/mL
Ampicillin	2–20 mg/mL
Amoxicillin	2–20 mg/mL
Ceftriaxone	2–20 mg/mL
Cefuroxime	2–20 mg/mL

† Skin prick tests were performed with the second dose only in patients with anaphylaxis in with the first dose before then. Intradermal tests were performed first with the first dose and if this was negative, with the second dose.

Drug Provocation Tests (DPT)

DPTs were carried out in hospital conditions in accordance with ENDA recommendations.[1,15] These tests were performed only in patients with negative skin tests, and not in patients with positive skin tests due to ethical concerns. The provocation test was accepted as positive in those who had skin findings, respiratory, cardiovascular, or gastrointestinal system findings, or changes in vital signs during or after the test. Patients with a history of late reactions were followed up for 5 more days with home treatment.[1,3]

Penicillin allergy

Patients with positive DAP test, penicillin G skin test and/or penicillin V provocation test, were accepted as penicillin allergy.

Aminopenicillin allergy

Patients with a positive skin test and/or provocation test with aminopenicillin and with negative DAP penicillin test, penicillin G skin test, negative oral penicillin V provocation were accepted as aminopenicillin allergy.[16]

Cephalosporin allergy

Patients whose sensitivity was shown with cephalosporin with a skin test or provocation tests and whose penicillin skin and provocation tests were found to be negative with all reagents were accepted as cephalosporin allergy.[16]

β-lactam cross reaction

The positive reactions of patients with penicillin (DAP penicillin, penicillin G, and aminopenicillin) and cephalosporin was classified as β-lactam cross-reaction.[2-4] We did not search to find a safe β-lactam in these patients.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences program (Version 23.0. Armonk, NY). Pearson Chi-square test or Fisher's exact test was used to comparing the categorized data. The normality of the distribution of continuous variables was evaluated with the Skewness-Kurtosis and the Kolmogorov Smirnov test or Shapiro Wilks test. Those who did not show normal distribution among continuous variables were given as median, interquartile range interquartile range (IQR [25–75th percentile]). Nonparametric tests were used to compare data that did not show normal distribution. Binary logistic regression analysis was performed to determined risk factors for β-lactam allergy. A value of $p<0.05$ was accepted to be statistically significant.

Results

Eighty-one children with suspected a β-lactam allergy were evaluated. The median age of the patients was 9 years.[5-13] Forty-six patients (56.8%) were male. Family history of drug allergy was determined in 15 (18.5%) of the patients.

The culprit drug was reported as aminopenicillin in 49 (60.5%), cephalosporin in 17 (21%), and benzathine penicillin G (BPG) in 15 (18.5%) patients (Table 2). In a great number of patients delayed reactions (56.8%) have been reported and maculopapular eruption (46.9%) was found to be the most common reaction type. Two (2.5%) of the patients had history of anaphylaxis (*n*=1 with BPG, *n*=1 with ceftriaxone). In the history of the patient who had anaphylaxis only with BPG, there were complaints such as mild itching, restlessness, and abdominal pain with the use of amoxicillin-clavulanate (AMC). These complaints were

Table 2. General characteristics of the patients and characteristics of penicillin allergy according to the history

Culprit drug	***n* (%)**
Aminopenicillins	49 (60.5)
Amoxicillin/Amoxicillin-clavulanate	41
Ampicillin-sulbactam	8
BPG	15 (18.5)
Ceftriaxone	14 (17.3)
Cefuroxime	3 (3.7)
The route of administration of the drug	
Parenteral	36 (44.4)
Enteral	45 (55.6)
Signs/symptoms leading to suspicion of β-lactam allergy	
Anaphylaxis‡	2 (2.5)
Urticaria-angioedema	23 (28.4)
Maculopapular eruption	38 (46.9)
Subjective symptom§	9 (11.1)
Skin test positivity (only in suspected BPG)	9 (11.1)
Chronology of the reactions	
Immediate (≤1 h)	35 (43.2)
Delayed (>1 h)	46 (56.8)
Time between reaction and allergic evaluation (months), median, (IQR)†	6 (4–8)
Asthma (±allergic rhinitis)	12 (14.8)

BPG: Benzathine penicillin G; IQR: interquartile range; †: Given as median and interquartile range; §: Non-specific findings refer to feeling unwell, or discomfort; ‡: Ceftriaxone and benzathine penicillin G.

attributed to AMC side effects and the drug was discontinued. The clinical characteristics of the patients are shown in Table 2.

Eleven of the patients were receiving BPG prophylaxis due to acute rheumatic fever for a median of 14 months.[13-21] Since these patients were suspected of having BPG allergy, their prophylaxis was performed with a median of 2 (3–5) months with non β-lactam antibiotic (azithromycin).

Allergic Evaluation

The median time between the patients' suspicious reactions and allergic evaluation was 6 (4-8) months. Drug skin test and provocation test results showed that 10 (12.3%) patients had sensitivity to a β-lactams (aminopenicillin *n*=7/49, BPG *n*=1/15, ceftriaxone *n*=2/14, cefuroxime *n*=0/3). Allergy diagnosis was excluded in all patients who received BPG prophylaxis with intramuscular administration of BPG. The diagnostic approach to patients with suspected β-lactam allergy is shown in Figure 1 as a flow diagram.

Of the patients whose diagnosis was confirmed (*n*=10), 6 had a history of immediate type reaction, 4 of them had a positive early reading in the skin test. The early and late readings of skin tests of all patients with late reactions were found to be negative. Patients with confirmed diagnosis were significantly older (*p*=0.031) and the rate of clinical immediate type reaction was higher (*p*=0.033) than in the tolerant group. The comparison of the clinical characteristics of patients with and without confirmed β-lactam allergy is shown in Table 3.

Two patients showed cross-reaction between penicillin and a cephalosporin (Table 4). One of these patients had a history of anaphylaxis after the use of BPG. The other patient had previously used oral AMC for tonsillopharyngitis and was treated later with parenteral AMP-s due to lack of clinical improvement. Immediately after the first dose of therapy, development ofurticaria-angioedema was described. In the skin tests of these two patients, a positive result was found with cefuroxime in addition to DAP penicillin. Clinical characteristics, drug skin tests, and the results of provocation tests of the patients with confirmed beta-lactam allergy are shown in Table 4.

In the regression analysis performed to determine the risk factors of patients with confirmed β-lactam allergy, older age (*p*=0.021, OR=1.27, 95% confidence interval: 1.03–1.55), presence of clinical immediate reaction (*p*=0.017, OR=7.1, 95% confidence interval: 1.42–36.03) was determined as a significant risk factor.

Discussion

the results of this study showed that 87.7% of children who were reported to be allergic to beta-lactam were actually not allergic. Moreover, we determined that the vast majority of patients were allergic to penicillin or cephalosporin group only and did not need to avoid the whole group.

Approximately 10% of parents report at least one β-lactam hypersensitivity in their children, and a much lower proportion of these are confirmed.[17-19] Consistent with this, our results showed that only 12.3% of the patients had

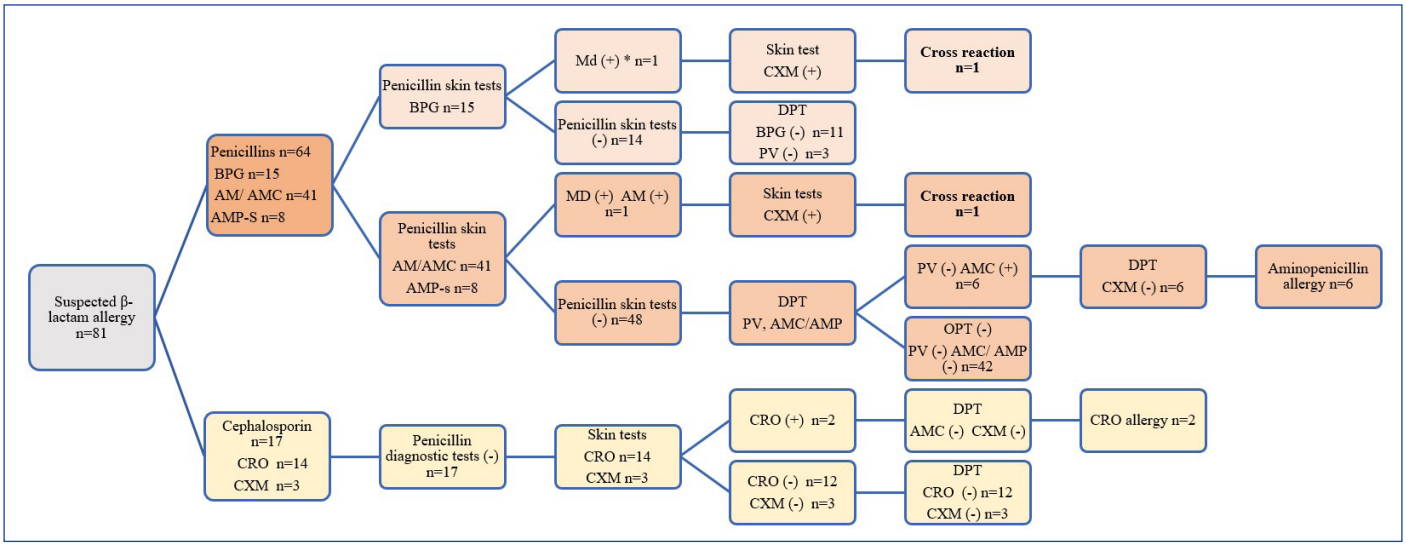

Figure 1. Diagnostic approach and test results for patients with suspected beta-lactam allergy. *There is urticaria with amoxicillin-clavulanate in the history. Positive in prick stage with minor determinant. AM: Amoxicillin, AMP: Ampicillin, AMC: Amoxicillin-clavulanate, AMP-S: Ampicillin-sulbactam. BPG: Benzathine penicillin G, CRO: Ceftriaxone, CXM: Cefuroxime; MD: Major determinants, Md: Minor determinant, PV: Penicillin V, DPT: Drug provocation tests, Penicillin V.

Table 3. Comparison of the clinical characteristics of the patients allergic and tolerant to β-lactam

	Allergic *n*=10 (12.3)	Tolerant *n*=71 (87.7)	*P*
Gender			
Male	6 (60)	40 (56.3)	0.827
Female	4 (40)	31 (43.7)	
Age, years, median † (IQR)	12 (9.5–15)	8 (5–12)	0.031
Suspected β-lactam			
Penicillin	8 (80)	56 (78.9)	0.935
Cephalosporin	2 (20)	15 (21.1)	
Culprit drug			
BPG	1 (10)	14 (19.7)	0.780
Aminopenicillin	7 (70)	42 (59.2)	
Ceftriaxone	2 (20)	12 (16.9)	
Cefuroxime	0	3 (4.2)	
Clinical immediate type reaction	6 (60)	19 (26.8)	0.033
Clinical presentations			0.002**
Anaphylaxis	2 (20)	0	
Urticaria angioedema	4 (40)	19 (26.8)	
Maculopapular eruption	4 (40)	34 (49.7)	
Subjective complaints‡	0	9 (12.7)	
Skin test positivity with BPG, before injection	0	9 (12.7)	
Time between reaction and tests, months, median†, (IQR)	5 (3–6)	6 (4–8)	0.235
The route of administration of the drug			
Parenteral	4 (40)	32 (45.1)	0.763
Enteral	6 (60)	39 (54.9)	
Having a family history of drug allergies	1 (10)	14 (19.7)	0.679*
Atopy in the child	1 (10)	13 (18.3)	1*

*: Fisher test was performed, **: Statistical significance is due to anaphylaxis, IQR: Interquartile range; †: Expressed as median and IQR; ‡: Non-specific findings refer to feeling unwell, or discomfort; BPG: Benzathine penicillin G.

β-lactam allergy confirmed. Although allergic reactions have been reported in the history, the fact that patients can actually tolerate these drugs can be explained in several ways; first, cutaneous reactions seen in the course of a viral or bacterial infection may be labeled as drug allergy incorrectly; second, the interaction of non-specific infection with a drug or its metabolites may lead to an enhanced immune reactivity, and non-persistent sensitization; third, the reaction may develop via non-immunologic mechanisms, and finally drug allergy may disappear over time.[1,3,20-23]

A detailed history and examination are the first steps in the evaluation of a patient with suspected drug allergy. However, allergic evaluation is often required for definitive diagnosis. The most commonly used tools for this purpose are drug skin tests and provocation tests.[17] One of the factors that directly affect the result in skin tests is whether the antigenic determinants of the tested drug are known. In this regard, commercial antigenic determinants for penicillin are available and the test has been validated. On the other hand, cephalosporins do not have a commercially available antigenic determinant, skin tests are done with intravenous preparations and are not as valid as penicillin tests. However, it has been reported that cephalosporin skin tests can be used in the diagnosis of immediate reactions.

The results of skin testing with β-lactams also depend on the time between the last allergic reaction and the tests and the clinical type of reaction. Our results showed that the drug skin test was significantly more positive in patients who reported immediate reaction, as expected. We did not provoke patients with positive skin tests due to ethical concerns, but we applied provocation tests to

all patients with negative skin tests. Therefore, our results are unlikely to be false negatives. On the other hand, we found a negative response in the skin tests of patients who reported late reactions, and we confirmed the diagnosis of these patients with oral provocation tests. Maculopapular eruptions are the most frequently reported clinical picture in drug reactions, and most of them are not true drug allergies. Since the skin tests are limited in the evaluation of these patients, it is recommended to complete the allergic evaluation by direct provocation, our results also support this.

According to our results, the most responsible agent was amoxicillin-clavulanic acid and the most common clinical presentation was maculopapular rash in the clinical picture. The relationship between the use of aminopenicillin and maculopapular reaction during the course of viral tonsillopharyngitis is well known. Most of these patients do not have permanent sensitization. In this respect, our results seem compatible with the literature.[16,24,25] A problem in evaluating patients with suspected aminopenicillin allergy is the fixed combinations of these drugs with β-lactamase inhibitors. β-lactamase inhibitors alone or in combination with aminopenicillin may cause sensitivity.[26] We did not make a separate allergic evaluation for β-lactamase inhibitors in our study. We could not find any difference between drugs in terms of diagnosis confirmation. However, diagnosis confirmation was higher in patients who reported clinical immediate reactions. On the other hand, allergy diagnosis was excluded in all patients with positive skin test before injection with BPG, and subjective complaints. This is particularly important in patients receiving BPG prophylaxis. Although it is not used frequently, BPG is an indispensable drug in the prophylaxis of patients with acute rheumatic fever. In these patients, drug allergy was excluded in all allergic evaluations due to the positive skin test performed before injection. Mislabeling "penicillin allergy" in these patients may increase the risk of rheumatic heart diseases.

Our data, as well as those in the literature, determined that different allergy test patterns can be seen in those with β-lactam allergy. In our country and European populations, a lower sensitivity to major determinant and minor determinant is reported with penicillin skin tests. This is related to the higher rate of amoxicillin/ampicillin allergy and the sensitivity of these patients to the R side chain.[16,19,25] This type of sensitization is called selective aminopenicillin allergy. If the drug that causes sensitization first is an aminopenicillin, the produced immunoglobulin (Ig) E mainly recognizes aminopenicillins.[24] If sensitization occurs with penicillin G, the produced IgE molecule can react to both aminopenicillins and other β-lactam antibiotics.[19] Delayed reactions are more likely to be selective. This sensitization profile is also related to the persistence of antibiotic allergy. Sensitization to side chains tends to be transient in a shorter time, sensitization to β-lactam core tends to persist longer. Similar to aminopenicillin allergy, cephalosporin allergies often develop against side chains.[4] The pattern of sensitization, which is a common result of genetic and environmental factors and antibiotic prescribing habits, shows distinct geographical differences. We found that only two patients were susceptible to both DAP penicillin and aminopenicillin at the same time by skin test and/or history Table 4 (patient 1 and 2). In addition, we found a positive reaction in the skin test of both patients with cefuroxime (Fig. 1). Although there is similarity at the side chain level between penicillin G and amoxicillin or ampicillin, it has not been reported with cefuroxime. Therefore, we thought that a common antigenic structure (such as β-lactam core) in penicillin and cephalosporin groups might have caused the sensitization, although we could not prove it in the laboratory.

Cross-reactions can occur between penicillins and cephalosporins due to the similarity at the side chain level or the same ring structure.[27] In previous data, the risk of cross-reaction between penicillins and cephalosporins, including meta-analyzes, was reported as a serious problem. The contamination of cephalosporin preparations with penicillin before 1980 is an important reason for this. Subsequent data blamed the similarity between R group of penicillins and R_1 of cephalosporins in these cross-reactions.[2,6,7,9] Nevertheless, the fact that there are identical or similar structures between penicillins and cephalosporins cannot be ignored. For this reason, it is appropriate to give priority to safer groups in antibiotic management until the diagnosis is confirmed, especially in immediate reactions, as serious pictures may develop in subsequent exposures.

Age, gender, family history of drug allergy, and atopy have been determined to be no risk for β-lactam allergy.[4] In our patient group, we identified older age and immediate clinical reaction as risk factors for confirmed drug allergy. We thought this might be due to the cumulatively increasing exposure to β-lactams with age.

Conclusion

Patients with suspected β-lactam allergy must be evaluated with detailed history and, if necessary, skin tests and provocation tests to confirm and classify drug allergy. It should be said that most of the patients can tolerate these drugs, and small number of patients whose diagnosis is

Table 4. Clinical characteristics of patients with confirmed β-lactam allergy

Patient number	Age and gender	Culprit drug	Clinical presentation	Drug skin tests					OPT			Confirmed β-lactam
				MD	PG	Md	AMP/AM	CXM	PV	AMP/AM	CXM	
Patients with confirmed penicillin allergy												
Immediate type reactions (penicillin G and aminopenicillin)												
1	9-F	BPG†	A	–	–	+	NP	+ §	NP	NP	NP	Penicillin and cephalosporin
2	11-F	AMP-s†	U-AE	+	–	–	+	+ §	NP	NP	NP	Penicillin and cephalosporin
3	10-M	AMC	U-AE	–	–	–	–	–	–	+	–	Aminopenicillin
4	13-M	AMC	U-AE	–	–	–	–	–	–	+	–	Aminopenicillin
Delayed type reaction (aminopenicillin)												
5	14-M	AMC	MPD	–	–	–	–	–	–	+	–	Aminopenicillin
6	9.5-F	AMC	MPD	–	–	–	–	–	–	+	–	Aminopenicillin
7	15-M	AMC	MPD	–	–	–	–	–	–	+	–	Aminopenicillin
8	7-F	AMC	MPD	–	–	–	–	–	–	+	–	Aminopenicillin
Cephalosporin immediate type reaction												
9	15-M	CRO	U-AE	–	–	–	–	+	–	–	–	Ceftriaxone
10	16-M	CRO	A	–	–	–	–	+	–	–	–	Ceftriaxone

A: Anaphylaxis, AM: Amoxicillin; AMC: Amoxicillin-clavulanic; AMP: Ampicillin; AMP-S: Ampicillin-sulbactam; BPG: Benzathine penicillin G; CRO: Ceftriaxone; CXM: Cefuroxime; E: Male; F: Female; MD: Major determinant; Md: Minor determinant; MPD: Maculopapular rash; OPT: Oral provocation test; PG: Penicillin G; PV: Penicillin V; U-AE: Urticaria angioedema; NP: Not performed; †: Regarding the parenteral application; §: Positive in intradermal test at a concentration of 2 mg/ml.

confirmed should avoid the whole β-lactam group because of cross-reactivity.

Disclosures

Ethics Committee Approval: The study was approved by the ethics committee of Erzurum Regional Training and Research Hospital on 05.11.2013 (No: 2013/70).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concep – A.S., A.I.Y.; Design – A.S., A.İ.Y., N.G.; Supervision – A.S., N.G., A.İ.Y.; Materials – A.S., A.İ.Y.; Data collection &/or processing – A.S., A.İ.Y.; Analysis and/or interpretation – A.S., A.İ.Y., E.Y., N.G., Z.T.; Literature search – A.S., A.İ.Y., N.G., E.Y., Z.T.; Writing – A.S., A.İ.Y., N.G., E.Y., Z.T.; Critical review – A.S., A.İ.Y., N.G., E.Y., Z.T.

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