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Suspected Reaction with Cephalosporin May Be a Predictive Factor for β-Lactam Allergy in Children

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Keywords
Hypersensitivity · Penicillin · Cephalosporin · β-Lactam allergy · Immediate reaction · Children · Skin test

Abstract
Background: Most children diagnosed with β-lactam allergy based only on history are not truly allergic, and mislabeling leads to use of less effective and more costly alternative broader-spectrum antibiotics, significantly increasing drug resistance. ***Objective:*** To determine the frequency and risk factors of confirmed allergy in patients with β-lactam allergy reported by parents or their doctors and evaluate cross-reactivity between β-lactams in children with confirmed allergy. ***Method:*** Sixty-seven children with suspected β-lactam allergy were evaluated via history, sIgE measurements, skin tests, and drug provocation tests over a period of 5 years. ***Results:*** β-Lactam allergy was confirmed in 10 (14.9%) patients. Six patients had a positive intradermal test result to one or more of the penicillin skin test materials or ceftriaxone, 4 patients with negative skin test results had positive test results with suspected drugs. Age, gender, time interval between evaluation and the initial reaction, personal history of atopy, parental history of drug allergy, reaction type, and multiple drug allergy history were not significantly different between allergic and tolerant patients. For culprit drugs, there was a significant different between the 2 groups; the rate of confirmed diagnosis was significantly higher for cephalosporins such as ceftriaxone, cefuroxime, and cefprozil ($p = 0.03$). Three patients with allergy to penicillin tolerated cefuroxime; in 4 patients with selective allergy to ceftriaxone tolerated cephalosporins with a dissimilar side chain (cefadroxil, cefuroxime, cefaclor, and cefdinir). ***Conclusion:*** Our study indicates that most patients with a suspected β-lactam allergy tolerated this drug. An appropriate diagnostic allergy workup may prevent the use of less effective and more expensive alternatives.
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Introduction

β-Lactam antibiotics are widely prescribed due to their broad bacterial spectrum and low toxicity [1]. Allergy to this group of antibiotics is frequently reported in children

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by parents or their physicians. The diagnosis of β-lactam allergy is often challenging because of questionable history and diagnostic workup, which is complex and sometimes risky. In daily practice, many children with a suspected allergy are labelled as being allergic to penicillin without an adequate allergological workup, leading to the use of less effective and more costly alternative broader-spectrum antibiotics and significantly increasing drug resistance [2–4]. Studies based on an allergological workup have shown that 12–60% of patients who report a β-lactam allergy have a true allergy [5–8]. In studies reporting a high rate of positivity, authors emphasize that physicians should acknowledge the importance of drug allergy history [9].

Although overlap between immediate and accelerated reactions has been reported, immediate reactions to β-lactam antibiotics occur within 1 h of administration and identification of this reaction is essential as it poses a subsequent risk of severe reactions [10]. Immediate reactions to β-lactam antibiotics can be assessed by history, skin tests including penicillin determinants (penicilloyl-polylysine [PPL], minor determinant mixture [MDM], and penicillin G), aminopenicillins (amoxicillin [AX] and ampicillin [AMP]) and culprit drugs, measurement of specific IgE (sIgE) to penicilloyl V, penicilloyl G, amoxicilloyl, and ampicilloyl, and drug provocation tests (DPT) if skin tests and/or sIgE are negative [11]. Skin testing with penicillin reagents (MDM and major determinant benzylpenicilloyl polylysine) has been shown to be safe and effective, with a high negative predictive value [12]. DPT involve controlled administration of a culprit drug, and they remain the gold standard for drug allergy workup [13].

Early studies in the 1960s and 1970s frequently estimated 10% cross-reactivity between penicillins and cephalosporins [14, 15]. This high rate of cross-reactivity has decreased since the 1980s. In later reports, approximately 1% of patients who were allergic to penicillin reacted to cephalosporins, likely due to the decrease in the use of first-generation cephalosporins, which have structures similar to that of penicillin [16–19]. In practice, although it has been shown to be incorrect, that overestimation has led to the avoidance of all β-lactam antibiotics if there is a history suggestive of penicillin allergy. An allergy to β-lactam antibiotics can be due to IgE antibodies against R chains or the common β-lactam ring [20, 21]. Cephalosporins have 2 side chains (R1 and R2); while the R2 side chain is lost after conjugation of the cephalosporins with the carrier protein, the R1 side chain remains bound to the carrier protein and is recognized by IgE [22]. Recent studies have shown that selective sensitization to the R1 side chain is a major factor for cross-reactivity between cephalosporins and aminopenicillins or among cephalosporins. A previous study reported that 38% of patients with a selective response to AX developed cross-reactivity to cefadroxil with identical side chains [23]. The presence of identical side chains contributes to high cross-reactivity between penicillin and cephalosporins, implying that a patient who is allergic to a β-lactam antibiotic can better tolerate another β-lactam antibiotic with dissimilar side chains than one with identical side chains [23, 24].

The aim of this prospective analysis was to identify: (1) the frequency of confirmed allergy in children with a history of immediate β-lactam allergy and factors affecting positive results, (2) the diagnostic accuracy of testing with all available penicillin determinants, and (3) assessment of cross-reactivity between β-lactams.

Methods

This prospective study was performed in the Department of Pediatric Allergy and Immunology of Kocaeli University (Turkey) from January 2012 to January 2017. All patients referred to our outpatient clinic with a history of immediate reaction to β-lactam antibiotics were included in this study. Exclusion criteria included a history suggestive of a nonimmediate reaction or a nonimmediate reaction to β-lactam, severe cutaneous adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, a drug reaction with eosinophilia, and systemic symptoms.

All of the patients completed a standard questionnaire and underwent an allergy workup based on European Network for Drug Allergy (ENDA) guidelines for immediate reactions to β-lactam [11]. sIgE to penicilloyl V, penicilloyl G, amoxicilloyl, and ampicilloyl was measured by using Uni CAP (Phadia AB, Uppsala, Sweden) in all of the patients before skin testing, and patients with negative results underwent skin tests (the lower limit of detection is 0.35 kIU/L).

A skin prick test (SPT) was performed initially, and an intradermal (ID) skin test was done if the result of the SPT was negative. A DPT with suspected β-lactams was performed in patients with negative SPT and/or sIgE results (except severe anaphylactic reactions). Patients with positive SPT and/or sIgE were not challenged and were advised to continue medication avoidance.

Skin Test Procedure

SPT was performed with all available penicillin determinants, including a major determinant (PPL, 5×10^{-5} M) and MDM (2×10^{2} M) (Diater Laboratories, Madrid, Spain), penicillin G (10,000 U/mL), AMP (25 mg/mL), AX-clavulanic acid (25 mg/mL), cefuroxime (2 mg/mL), ceftriaxone (2 mg/mL), and cefazolin (2 mg/mL). The SPT was considered positive when a wheal accompanied by erythema was 3 mm greater than the negative control (saline solution) if the response to histamine (10 mg/mL) was positive after 20 min. If the SPT responses were negative, 0.02 mL of

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Table 1. Clinical characteristics and test results of patients diagnosed with β-lactam allergy

Patient No.	Age, years	Sex	Culprit drug	Reaction	Skin test result	Challenge with culprit drug	DPT with alternative drug
1	10.83	F	AX-CLV	Anaphylaxis	ID with MDM: positive SPT and ID with AX-CLV/ampicillin: negative	Not done	Cefuroxime axetil: negative Cefixime: negative
2	2.5	F	AX-CLV	Urticaria	ID with MDM/PPL/penG: positive SPT and ID with AX-CLV/ampicillin: negative	Not done	Cefuroxime axetil: negative
3	12.66	F	Cefuroxime axetil	Urticaria	SPT and ID with PPL/MDM/penG: negative SPT and ID with AX-CLV/ampicillin: negative SPT and ID with cefuroxime: negative	DPT with cefuroxime axetil: urticaria	Cefixime: negative Cefpodoxime: negative Penicillin V: positive Cefdinir: positive
4	3.5	M	Cefprozil	Anaphylaxis	ID with MDM/ PPL/penG: positive SPT and ID with AX-CLV/ampicillin: negative	Not done	Not done
5	10	F	Benzyl-penicillin	Angioedema	SPT and ID with PPL/MDM/penG: negative SPT and ID with AX-CLV/ampicillin: negative	DPT with penicillin V: urticaria	Cefuroxime axetil: negative Cefazolin: negative
6	4.9	M	Ceftriaxone	Urticaria-angioedema	SPT and ID with PPL/MDM/penG/ceftriaxone: negative SPT and ID with AX-CLV/ampicillin: negative	DPT with ceftriaxone: urticaria	Penicillin V/AX-CLV: negative Cefuroxime axetil: negative
7	4.8	M	Ceftriaxone	Urticaria	SPT and ID with PPL/MDM/penG: negative SPT and ID with AX-CLV/ampicillin: negative SPT and ID with ceftriaxone: negative	DPT with ceftriaxone: urticaria	Penicillin/AX-CLV: negative Cefuroxime axetil: negative Cefdinir: negative Cefaclor: negative
8	9.5	F	Ceftriaxone	Anaphylaxis	SPT and ID with PPL/MDM/penG: negative SPT and ID with AX-CLV/ampicillin: negative ID with ceftriaxone: positive	Not done	Penicillin/AX-CLV: negative Cefuroxime axetil: negative Cefadroxil: negative
9	11.7	F	Ceftriaxone	Urticaria	ID with MDM: positive SPT and ID with PPL penG/AX-CLV/ampicillin: negative SPT and ID with ceftriaxone: negative	Not done	Not done
10	7.4	M	Ceftriaxone	Anaphylaxis	SPT and ID with PPL/MDM/penG: negative SPT and ID with AX-CLV/ampicillin: negative ID with ceftriaxone: positive	Not done	Penicillin V: negative Cefuroxime axetil: negative Cefadroxil: negative

CLV, clavulanate; penG, penicillin G.

serially diluted (1/100; 1/10) and undiluted reagents was injected intradermally on the volar forearm and the injected-area wheal was marked. Positive results were defined as a wheal 3 mm greater than the diameter of the injected.

Drug Provocation Test

DPT were performed by administration of increasing oral doses of the culprit drug every 30 min up to the full therapeutic dose according to ENDA guidelines [13]. The outcome of the challenge was recorded as positive at any time during the challenge when symptoms appeared and the challenge was stopped and the reaction treated accordingly. If no symptoms appeared, the challenge was recorded as negative. Patients were monitored for at least 2 h after the last dose. If the open challenge was negative on day 1, the involved drug was given the day after challenge at home and continued for 5 days. Patients were asked to contact the clinic if there was a delayed reaction.

Assessment of Cross-Reactivity

In patients who had confirmed allergy to a β-lactam antibiotic, we performed additional DPT with another β-lactam antibiotic for assessment of cross-reactivity. Patients allergic to penicillins were given cephalosporins with different side chains. Patients allergic to cephalosporin who had a negative result with a penicillin determinant were given penicillin V and/or AX-clavulanate and cephalosporins with different side chains.

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Table 2. Comparison of clinical and laboratory profiles in children with a confirmed allergy and tolerant to β-lactams

	Confirmed allergy	Tolerant	*p* value
Age at onset, years	7.79±3.65	6.89±3.90	0.365
Females	6 (60)	34 (59.6)	0.309
Males	4 (40)	23 (40.4)	
Time between reaction and evaluation, months	13.30±17.98	18.78±28.37	0.596
Atopy	4 (40)	19 (33.3)	0.726
Family history of drug allergy	2 (20)	4 (7)	0.217
Multiple drugs	0 (0)	9 (15.8)	0.335
Type of reaction			0.283
Anaphylaxis	4 (40)	5 (8.8)	
Urticaria	5 (50)	40 (70.2)	
Angioedema (without urticaria)	1 (10)	5 (8.8)	
Other	–	7 (12.2)	
Culprit drug			0.03
Penicillin	1 (10)	6 (10.5)	
Aminopenicillin	2 (20)	34 (59.6)	
Cephalosporin	7 (70)	17 (29.8)	

Values are presented as mean ± SD or numbers (%).

Statistical Analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) for Windows version 15 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± SD (or medians [range]) and categorical variables were expressed as numbers (%). The Mann-Whitney U test was used to compare numerical variables and Fisher's exact test was used to compare categorical variables between groups. The data were examined using 95% CI, and $p < 0.05$ was considered statistically significant.

Results

Clinical Characteristics of the Study Population

Sixty-seven children with a suspected β-lactam allergy were included in this study. The median age of the patients was 7.08 years (range 1–17.33). AX-clavulanate was the most commonly reported drug (53.7%). The most common clinical manifestation was urticaria (55.2%). Nine patients (13.4%) reported reactions to more than one β-lactam. In total, 23 children (34.3%) had a personal history of allergic disease and 6 patients (9%) had a parental history of β-lactam allergy.

Clinical Characteristics and Cross-Reactivity of Confirmed Allergy to β-Lactams

Ten out of 67 patients (14.9%) were diagnosed as having a true allergy to β-lactams. All of these patients had negative results on SPT and serology (sIgE for penicilloyl V, penicilloyl G, amoxicilloyl, and ampicilloyl). The 6 patients had a positive ID test result to one or more of the penicillin skin test materials (PPL, MDM, or PG) or ceftriaxone. None of the patients had a positive SPT or ID test to AMP or AX-clavulanic acid. One patient experienced generalized urticaria during an ID test. Four patients who had a negative skin test result had positive test results with the suspect drug. All of these patients experienced urticaria during the challenge. The clinical characteristics and the results of the tests for patients diagnosed as having β-lactam allergy are summarized Table 1.

The 6 patients with a history of reaction to penicillin or cephalosporin had positive skin test results with a penicillin determinant or positive DPT results with penicillin V and were considered as cross-reactive. Among the cross-reactive patients, 3 patients (patients 1, 2, and 5) who had a reaction to penicillin had negative skin test results to cefuroxime and tolerated this drug (1 also tolerated sefixime and 1 also tolerated cefazolin). The 1 patient (patient 3) who had a reaction to cefuroxime developed a reaction to penicillin V on provocation and 2 patients (patients 4 and 9) who had a reaction to cefprozil and ceftriaxone had a positive skin test result for the penicillin (DPT is not performed for penicillin) determinant. All 4 patients (patients 6, 7, 8, and 10) who had reactions to ceftriaxone tolerated penicillin V. To determine safe alternative drugs in 5 patients allergic to cephalosporin (4 of these patients had a selective allergy to cephalosporin),

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we also challenged with one or more of the following substances: cefuroxime, cefaclor, cefdinir, cefodroxil, cefixime, and cefpodoxime, which have a different R1 side chain than the suspect cephalosporin. Eight DPT with dissimilar cephalosporins were performed in patients with a selective cephalosporin allergy; there were no reactions.

Comparison of Allergic and Nonallergic Patients

The patients allergic to β-lactams were compared with those who were tolerant, and there were no significant differences in terms of age, gender, the interval between the evaluation and the initial reaction, presence of atopy, parental history of β-lactam allergy, reaction severity, and multiple drug allergy history. Considering the culprit drug, there was a significant different between the 2 groups; the diagnosis of β-lactam hypersensitivity was significantly higher in patients who reported reactions to cephalosporins ($p = 0.03$). Comparison of the clinical and laboratory profiles of the children with a confirmed allergy and tolerant to β-lactams is given in Table 2.

Discussion

In the present study, we evaluated children with suspected immediate allergic reactions to β-lactams according to the ENDA diagnostic protocol over a 5-year period and found that 85.1% of the patients tolerated β-lactams. These findings are similar to the results of previous studies [6, 21, 25] and highlight the significance of a confirmed diagnosis of β-lactam allergy.

In our study, 6 patients had a positive reaction to a skin test, and 4 of the 61 patients who had negative skin test results and/or sIgE had positive challenge results. We have confirmed a high negative predictive value (93.4%) for the ID skin test. Caubet et al. [26] reported 91.5% specificity and 66.7% sensitivity for ID skin tests, and Fox and Park [27] also reported a negative predictive value >95%. DPT is the gold standard to confirm allergy or tolerance to β-lactam antibiotics but this procedure is time consuming and the patient needs to be closely monitored for symptoms in a hospital setting with expert staff [13]. The penicillin skin test is easy to perform and may be useful to reduce the number of challenges. As in previous studies [26, 28], we found that the sensitivity of the skin test is not high; hence, a provocation test is recommended for patients who have negative penicillin skin test results.

Previous studies have reported a 9–11% systemic reaction when skin testing is performed for β-lactams [29, 30], but in our study only 1 patient had a mild reaction (1.5%). Our study supports the studies by Valyasevi and Van Dellen [31] and Ponvert et al. [25], which reported lower rates than the previous studies.

In our study, age, gender, personal atopy, parental history of drug allergy, time interval between reaction and evaluation, type of reaction, and multiple drug allergy history were not related to confirmed β-lactam allergy as shown previously [6, 7].

An important finding of our study is that 29.1% of the children with suspected immediate allergic reactions to cefalosporins had a confirmed allergy. Previous studies reported rates of confirmed allergy to cephalosporins of 50 and 76.7% [6, 8]. Recently, in a French Allergy Vigilance Network report of severe drug allergy, of all of the β-lactams involved, 27% were cephalosporins [32]. In a study based on total antibiotic use data for 13 non-European Union countries, the highest total cephalosporin use was noted for Turkey (33.4% of total antibiotic use) [33]. This finding highlights the importance of rational use of antibiotics; physicians should be aware of the many potential adverse effects of broader-spectrum cephalosporins in children, especially hypersensitivity reactions. We think that the use of parenteral cephalosporins such as ceftriaxone, which is known as a higher sensitizing route, as culprit drugs in the history may be predictive of confirmed β-lactam allergy, and detailed further multicenter studies are needed.

The reported cross-reactivity with cephalosporin in patients allergic to penicillin is approximately 10% [34–37]. A large study by Atanasković-Marković et al. [5] reported that cross-reactivity depends on the generation of cephalosporins and varies between 0.3% (ceftriaxone) and 23.9% (cephalexin). Another study did not find a significant difference in the rate of cephalosporin allergy between patients with a negative penicillin skin test result and positive individuals [38]. In a meta-analysis by Pichichero and Casey [39], cross-reactivity to cephalosporins in patients allergic to penicillin or AX was 2.63% and the authors found increased cross-reactivity with first-generation cephalosporins (cephalothin, 2.5%; cephaloridine, 8.74%; and cephalexin, 5.78%), second-generation cephalosporins (1.13%), and third-generation cephalosporins (0.45%). Our 3 patients who had a reaction to penicillin (2 patients to AX-CLV and 1 patient to benzylpenicillin) tolerated cefuroxime, a second-generation cephalosporin with a different side chain from penicillin. Our finding supports that, in patients with a penicillin allergy, if possible, skin tests should be performed with a cephalosporin with a different side chain from the re-

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sponsible penicillin, and patients who have negative results to skin tests should undergo a challenge.

With regard to patients allergic to cephalosporin, 3 patients who had a reaction with cefuroxime, cefprozil, and ceftriaxone had cross-reactivity to benzylpenicilline (2 patients had positive results for penicillin skin tests and 1 patient did not tolerate penicillin V).This result is closer to the results of a study by Romano et al. [8] who found 32.5% skin test or sIgE positivity to penicillin reagents (PPL, MD, BP, AM, and AMX) in patients with cephalosporin allergy (54.5% for patients with a cefaclor allergy). Atanasković-Marković et al. [5] found that in patients who had a reaction to cefaclor, cephalexin, ceftriaxone, and cefotaxime the frequency of cross-reactivity to benzylpenicilline was 85.4, 85.2, 57.1, and 100%. In our study, 4 patients with a selective ceftriaxone allergy underwent DPT with cephalosporins such as cefadroxil, cefuroxime, cefaclor, and cefdinir and none of them had a positive reaction. These findings indicated that 3 patients may be reactive to the β-lactam ring, and non-β-lactam antibiotics or desensitization should be used in these patients. For patients with a selective cephalosporin allergy, alternative cephalosporins with a different side chain can be administered by challenge after skin tests if possible.

In our study none of the patients were confirmed to have a penicillin allergy by means of positive sIgE to penicilloyl V, penicilloyl G, amoxicilloyl, and ampicilloyl, which was measured using Uni CAP. We performed firstly an in vitro test, because it is less expensive, less time consuming, and poses no risks for patients. However, these tests are of limited value. In previous studies, immunoCAP has been proven to be less sensitive than skin tests [25, 40].

A penicillin skin test, in combination with a consistent history, is generally a safe and reliable procedure in children with a suspected immediate β-lactam allergy, but the sensitivity of penicillin skin tests is not 100%; provocation tests are necessary in the case of negative skin tests. An appropriate diagnostic allergy workup will avoid the use of less effective and more expensive alternatives. Clinical evaluation of patients who report an aminopenicillin or a cephalosporin allergy should include two steps. Firstly, a skin test with penicillin determinants and the suspect drug and a provocation test with the suspect drug (if the skin test is negative) should be performed to confirm allergy. Secondly, a skin test with other β-lactam antibiotics with dissimilar side chains and a provocation test (if the skin test is negative) should be performed to determine if it is a selective allergy. Thus, a diagnosis of a selective allergy according to the side chain avoids labelling the patient as being allergic to all β-lactam antibiotics and the resulting overuse of antibiotics that are less effective and more expensive in the future.

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Statement of Ethics

The authors have no ethical conflicts to disclose. Informed consent was obtained from the parents of the patients. The local ethics committee on human research in Kocaeli University approved the study design and protocol.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

I.E.S. and M.A. designed this study, I.E.S. analyzed all of the data and wrote the first drafts of this paper, and I.E.S. and M.T.C performed the skin tests and DPT. All of the authors reviewed this paper.

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