



## Original Research

# Evaluation of Cross-Reactivity Between Penicillins and Cephalosporins in Children with a History of Cephalosporin Allergy

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### Abstract

**Objectives:** The cross-reactivity problem between cephalosporins and penicillins has mainly been evaluated in the context of patients allergic to penicillins. However, we have little data regarding the opposite aspect of the problem, i.e. the cross-reactivity in subjects primarily sensitized to cephalosporins. This prospective study aims to evaluate the cross-reactivity to penicillins and some other cephalosporins in patients with immediate allergic reactions to cephalosporins.

**Methods:** The study included 21 children with immediate allergic reactions to at least one cephalosporin. Skin testing was performed with a panel of minor and major determinant mixtures of penicillins and three commonly used cephalosporins (cephazolin, cefuroxime and ceftriaxone).

**Results:** The children had used  $5.14 \pm 4.91$  (1-15) times any beta-lactam antibiotic in the previous year and the most common cephalosporins accused were ceftriaxone (42.92%), and cefuroxime, cefazolin, cefixime, cefprozil and cefotaxime (9.5% each). Skin tests were positive for any cephalosporin in 14 (66.7%) subjects and penicillin allergens in 15 (71.4%) subjects. Totally, 85.7% of children with a positive allergy history to cephalosporins were found to be sensitive to either penicillin or any one of three cephalosporins.

**Conclusion:** There seems to be a high risk of adverse reactions to penicillins and other cephalosporins in children with a history of type I hypersensitivity reaction to cephalosporins. Therefore, skin testing with both cephalosporins and penicillins should be performed in patients with a history of cephalosporin allergy.

**Keywords:** Beta-lactams, cephalosporins, penicillins

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Beta-lactams constitute a group of antibiotics that has taken place in the treatment of many severe and non-severe infections for many years.<sup>[1]</sup> However, allergic reactions, especially to penicillins and cephalosporins, have significantly limited the widespread use of these drugs.<sup>[2]</sup> Cephalosporins, as an important member of these antibiot-

ics have become the most commonly prescribed antibiotics in recent years to which fear of allergy to penicillins also contributed. However, the widespread use of these antibiotics has resulted in sensitization of many people to these antibiotics leading to mild to severe allergic reactions.<sup>[3,4]</sup>

On the other hand, development of cross-reactions among

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beta-lactams have also been researched extensively in recent years, despite most of these studies have focused most commonly on cephalosporin sensitivity in subjects, especially in adults with penicillin allergies. We don't know the probability of tolerance of penicillins and cephalosporins by the patients who are allergic to some other cephalosporins because there are few studies on this subject.

This study aims to investigate cephalosporin and penicillin sensitivity in children with a history of cephalosporin allergy.

## Methods

The study comprised children who have a history of allergic reactions to cephalosporins admitted to pediatric outpatient department. Our study was conducted in accordance with the Declaration of Helsinki. After receiving approval from the Sisli Etfal Training and Research Hospital ethical committee (Approval number: 57), the study objectives were explained to parents and older children, and written consent was obtained. The names, dosages and administration routes of cephalosporins which had led to the reactions in addition to occurring time and type of reactions were learned from the parents. Skin prick tests have been performed at least one month after the allergic reactions, with antihistamines discontinued at least ten days prior to the tests. Skin prick tests were performed by a pediatric allergist under appropriate emergency conditions at the hospital, accompanied by trained personnel. Penicillin sensitivity was documented using benzylpenicillin polylysine (PPL) and minor determinant mixture (MDM) initially. For this, DAP PPL (PPL-D; final concentration:  $1.07 \times 10^{-2}$  mmol/L), Diater S.A. (Madrid, Spain), MDM (MDM-D, benzylpenicillin, sodium benzylpenicilloate and benzylpenicilloic acid; final concentration: 1.5 mmol/L) were used. PPL was used at the concentration of 7 nm/ml. MDM consisted of benzylpenicillin 1.7  $\mu$ mol/ml and benzylpenicilloic acid 1.3  $\mu$ mol/ml. Skin prick tests were performed on the forearm using a Stallerpoint needle (Stallergenes, France). A positive response was recorded if the mean diameter of the wheal was  $\geq 3$  mm and the negative control was non-reactive. If there was a negative response to prick tests, intradermal tests were performed. We used 0.02 mL of solutions for intradermal tests. Swelling larger than 5 mm with erythema within 20 minutes was defined as positive. If a positive response was obtained to any test performed with PPL or MDM, the case was considered to be sensitive to penicillin.

For cephalosporin sensitivity, skin prick and intradermal tests were performed with three commonly used antibiotics in Türkiye: Cephazoline (Sefazol<sup>®</sup> 500 mg vial), cefu-

roxime (Zinnat<sup>®</sup>) and ceftriaxone (Rocephin<sup>®</sup>) at a concentration of 2 mg/mL in 0.9% NaCl were used. During the test, histamine 10 mg/mL was used as positive control and 0.9%NaCl was used for negative control. In intradermal tests with cephalosporins utilized 1/100, 1/10, and 1/1 concentrations sequentially.

## Statistical Analysis

The study data was analyzed using "NCSS PASS 2007 & 2008 Statistical Software (Utah, USA)". Mann-Whitney U test was used for the analysis of abnormal distribution parameters and Fisher's Exact Chi-square and Chi-square tests for the analysis of qualitative data. McNemar's test was used to assess the significance of the difference between two allergens. A p-value less than 0.05 was considered statistically significant.

## Results

The study consisted of 21 children aged 6 months to 14 years (mean  $5.59 \pm 4.33$  years) 12 of which (57%) were girls. The children had used  $5.14 \pm 4.91$  (1-15) times any beta-lactam antibiotic in the previous year and ceftriaxone was the most commonly used cephalosporin (42.92%), followed by cefuroxime, cefazolin, cefixime, cefprozil, cefotaxime (9.5% each) and cephalixin and cefaclor (4.8% each). Amoxicillin plus Clavulanate was the most commonly used beta-lactam antibiotic other than cephalosporins. The reactions had occurred in about 1.8 minutes to 120 hours (mean  $26.87 \pm 31.40$  hours) of antibiotics use. The most common symptoms and signs seen in children were urticaria in 85.7%, angioedema in 38.1%, itching in 33.3%, vomiting in 23.8%, wheezing in 4.8% and anaphylaxis in 4.8% of children (Table 1). The antibiotics had been used via intramuscular route in 42.8%, oral route in 28.6%, and intravenously in 28.6% of children. Fifteen subjects had only one episode induced by a cephalosporin and 6 subjects had experienced two or more symptomatic episodes (urticaria in all of them).

Skin tests were positive for PPL or MDM in 15(71.4%) children with cephalosporin allergy. Overall, 14 cases (66.7%) were sensitive to one or more cephalosporins. Tests with

**Table 1.** Clinical data of the children allergic to cephalosporins

Clinical sign	Number	%
Urticaria	18	85.7
Angioedema	8	38.1
Itching	7	33.3
Vomiting	5	23.8
Wheezing	1	4.8
Anaphylaxis	1	4.8

ceftriaxone were positive in 11 children (52.3%), with cefazolin in 10 children (47.6%) and with cefuroxime in 8 children (38.1%) ( $p>0.05$ ). Eight of 10 children of cefazolin-sensitive group (80%), six of 8 subjects of cefuroxime-sensitive group, and eight of 11 ceftriaxone-sensitive group were also susceptible to penicillin (Table 2) ( $p>0.05$ ). In general, 85.7% of children with a positive allergy history to cephalosporins were found to be sensitive either to penicillin or any one of three cephalosporins.

## Discussion

The true incidence of penicillin and cephalosporin allergy among subjects with positive histories is approximately 10% or less and 1.0% to 2.8%, respectively.<sup>[5, 6]</sup> The most common hypersensitivity reactions to cephalosporins are probably directed at the R-group side chains rather than the core beta-lactam portion of the molecule.<sup>[7]</sup> The frequency of cephalosporin cross-reactivity in a penicillin-allergic patient is reported to range anywhere from 7% to 18% of subjects.<sup>[6]</sup> This reality has been documented with many studies evaluating cephalosporin allergy in penicillin-allergic subjects in recent years and according to current data there is no reason for concern regarding the cross-reactivity between cephalosporins and penicillins in penicillin-allergic subjects.<sup>[8, 9]</sup>

But in real life, the safety of administering a cephalosporin to subjects with a penicillin allergy history continues to be an area of controversy among physicians and a matter of considerable concern among subjects.<sup>[10, 11]</sup> So, current guidelines recommend that all subjects with a positive penicillin history should undergo penicillin skin testing before cephalosporin administration.<sup>[12]</sup> On the other hand, although current guidelines recommend that subjects with a history of an immediate-type reaction to a cephalosporin should undergo penicillin skin testing, we have inadequate data for the opposite condition, i.e. the use of penicillins in subjects primarily sensitized to cephalosporins<sup>[13]</sup>, especially in children.

Negative test results with accused cephalosporins in addition to positive results with penicillin antigens and some other cephalosporins (such as in our children number 9 and 18) may be due to excessive consumption of beta-lactams leading to silent sensitization of these subjects.<sup>[14, 15]</sup>

Cross-reactions have been reported especially between first-generation cephalosporins and penicillins rather than second and third-generation cephalosporins.<sup>[16, 17]</sup> In our study cross-reactivity has been found among penicillins and all three generations. This may be due to independent sensitization to all these antibiotics primarily rather than cross-reactivity, because of the common use of beta-lactam antibiotics and silent sensitization in our society.<sup>[14, 15]</sup>

Although we couldn't have done this due to ethical reasons, to document the true sensitization and cross-reactivity among our subjects we should have tested with all accused and non-accused beta-lactams (such as cefaclor, ampicillin and amoxicillin). For, allergic cross-reactivity between amoxicillin and cephalosporins that share identical R-group side chains is higher than for subjects with positive penicillin skin test responses. For example, 12% to 38% of subjects proved to be selectively allergic to amoxicillin have reacted to cefadroxil.<sup>[18]</sup> Similarly, subjects with ampicillin allergy are more allergic to cephalixin, cefaclor, cephadrine, cephaloglycin, and loracarbef.<sup>[19]</sup> A study evaluating cases with cephalosporin allergy concluded that cross-reactivity with aminopenicillins was the most frequent pattern of cross-reactivity.<sup>[20]</sup>

## Conclusion

Our results suggest that there is a high risk of adverse reactions to penicillins and other cephalosporins in children with a history of type I hypersensitivity reaction to cephalosporins. Therefore, skin testing with both cephalosporins and penicillins should be performed in patients with a history of cephalosporin allergy.

**Table 2.** The culprit drugs and skin prick test results of the subjects

Subject No.	Culprit drug	PPL	MDM	CFZ	CFR	CFX
1	CFX	+	-	+	-	+
2	CFX	-	-	-	-	+
3	CFX	+	-	-	-	-
4	CFX	-	-	+	+	+
5	CFX	+	-	+	-	-
6	CFX	+	-	-	+	+
7	CFX	-	+	-	-	-
8	CFX	+	-	-	-	-
9	CFX	-	+	+	-	+
10	Cefixime	+	-	-	-	-
11	Cefixime	+	-	+	-	+
12	Cephalexin	-	-	-	-	-
13	Cefotaxime	-	-	+	+	+
14	Cefotaxime	+	-	+	+	+
15	Cefaclor	-	-	-	-	-
16	Cefprozil	+	-	+	+	-
17	Cefprozil	+	-	-	+	-
18	CFZ	-	+	+	-	+
19	CFZ	-	-	-	-	-
20	CFR	+	-	-	+	+
21	CFR	+	-	+	+	+

PPL: Benzylpenicillin polylysine; MDM: Minor determinant mixture; CFZ: Cephazoline; CFR: Cefuroxime; CFX: Ceftriaxone.

## Disclosures

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