

Evaluation of Clinical Properties and Diagnostic Test Results of Cephalosporin Allergy in Children

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Keywords

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Abstract

Introduction: Beta-lactams (BLs) are one of the most frequent causes of drug hypersensitivity reactions (HRs), and cephalosporins are a widely used subclass of BLs, especially in children. The aim of this study was to evaluate the clinical features and diagnostic test results of pediatric patients evaluated for suspected cephalosporin allergy. **Methods:** This study included patients who presented to our pediatric allergy clinic with a history of reactions attributed to cephalosporins between January 1, 2011, and December 31, 2019, and whose diagnostic tests were completed for the diagnosis. **Results:** This study included 120 pediatric patients and 69 (57.5%) of them were girls. The median age was 38.63 (interquartile range 10.5–85.7) months. Reactions occurring within 1 h of drug intake were reported in 33 patients (27.5%). Reactions were maculopapular rash in 55 (45.8%) patients, urticaria and/or angioedema in 49 (40.8%), anaphylaxis in 11 (9.2%), severe cutaneous drug reaction in 4 (3.3%), and fixed drug reaction in 1 patient (0.83%). The most frequently sus-

pected agent was cefixime in 41 patients (34.2%). In total, 30 (25%) patients were diagnosed as having cephalosporin hypersensitivity. Confirmation of HRs was also significantly more frequent among patients who were older ($p: 0.000$), who had taken the drug parenterally ($p: 0.000$) and with immediate reactions ($p: 0.000$). **Conclusion:** Cephalosporin allergy has been confirmed in approximately one-fourth of the patients evaluated for suspected cephalosporin allergy. Confirmation of HRs was significantly more common among patients who were older, had immediate reactions, and had taken the drug parenterally.

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Introduction

Beta-lactams (BLs) are one of the most frequent causes of drug hypersensitivity reactions (HRs), and cephalosporins are a widely used subclass of BLs, especially in children [1]. The incidence of cephalosporin allergy is reported to be 1–3% in the general population and in the

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USA, with a significant increase in prevalence in the last 20 years across all age-groups [2–5].

Cephalosporins can cause both IgE-mediated and T-cell-mediated drug HRs. Immediate reactions are those that occur within 1 h of taking the culprit drug and can range from simple skin involvement to severe anaphylaxis [1, 6]. Nonimmediate reactions ranging from maculopapular exanthemas to severe cutaneous adverse drug reactions (SCARs) can appear after the first hour following drug intake [1]. In immediate reactions, symptoms are generally limited to the skin, and the most common clinical manifestation of nonimmediate reactions is maculopapular exanthema [7].

The core of both penicillin and cephalosporins consist of a four-membered BL ring. In penicillins, this BL ring is connected to a 5-membered thiazolidine ring, whereas in cephalosporins it is connected to a 6-membered dihydrothiazine ring [8, 9]. In the literature, it was reported that cross-reactivity to the common BL ring was very rare in IgE-mediated HRs [10]. While both penicillin and cephalosporins have an R1 side chain, cephalosporins have an additional R2 side chain. The R1 side chain is the major factor for cross-reactivity between cephalosporins and penicillins [8, 11]. Cross-reactivity between cephalosporins is rare and is due to similarity in the R1 or R2 side chains [11].

In the literature, studies mostly gave confirmation rates of BL-group antibiotic hypersensitivity. Studies reporting the confirmation rates and clinical features of cephalosporin allergies especially in childhood are limited. The aim of this study was to evaluate the clinical features and diagnostic test results of pediatric patients evaluated for suspected cephalosporin allergy.

Materials and Methods

This study included patients who presented to our pediatric allergy clinic with a history of reactions attributed to cephalosporins between January 1, 2011, and December 31, 2019, and whose diagnostic tests (skin tests [STs] and/or drug provocation test [DPT]) were completed for the diagnosis. As provocation tests could not be performed for patients with a history of SCARs, patients who had at least 1 skin test were included. This study was approved by the Ethics Committee of Ankara City Hospital (E1-20-456).

The initial drug allergy workup started with the standardized European Network of Drug Allergy (ENDA) questionnaire for drug allergy [12]. A detailed history was obtained, including spectrum and timing of symptoms, dose and route of administration of the suspected drug, list of concomitant medications, history, and timing of previous HRs, and physical examination findings. The patients' symptoms were classified according to medical records or their guardians' descriptions.

Urticaria, angioedema, bronchospasm, and anaphylaxis reactions were classified as immediate if they occurred within the first hour of drug administration. Reactions occurring more than 1 h after drug administration were classified as nonimmediate reactions.

Skin Prick, Intradermal, and Patch Tests

SPT and IDT with immediate readings were used to evaluate immediate HRs; PT was used for nonimmediate reactions. It was decided according to the clinical features and reaction history whether SPT or IDT should be applied. Patients who reported mild cutaneous reactions and delayed urticaria symptoms underwent DPT without prior skin testing in accordance with the latest EAA-CI position article [13]. However, STs were performed on some patients whose reported symptoms consistent with IgE-mediated reaction, even when the reaction occurred between 1 and 6 h after drug administration. Written informed consent was obtained from the patients' legal guardians.

SPT and IDT were performed with penicillin and the suspected drug [7, 14]. The classic penicillin test was done with the major determinant benzylpenicilloyl poly-L-lysine and minor determinant mixture (DAP kit, Diater, Madrid, Spain), penicillin (10,000 IU/mL), and amoxicillin-clavulanate (20 mg/mL). This was followed by STs with the suspected drug at the suggested concentration (2 mg/mL) [7]. All drugs were initially tested on the volar forearm skin using the prick method, and reactions were considered positive when a wheal diameter of at least 3 mm larger than that of the negative control with surrounding erythema was present 20 min later. The procedure was discontinued if a positive result was obtained. If SPT yielded negative results, 0.02 mL of the relevant agent was injected intradermally in the volar forearm skin. Readings were made 20 min after injection. Results were considered positive when an increase >3 mm in wheal diameter accompanied by erythema was present. Histamine 10 mg/mL was used as a positive control in SPT, and 0.9% NaCl solution was used as a negative control in SPT and IDT.

Patients with reported nonimmediate reactions were subjected to PT at least 6 weeks after resolution of symptoms. In cases of drug reaction with eosinophilia and systemic symptoms (DRESS), PTs were performed at least 6 months after the disease resolved. In accordance with the ENDA guidelines, the PT was performed using homogeneous mixtures of each drug at the suggested concentration in petrolatum (solid Vaseline), which were placed in aluminum chambers (Finn chambers) and adhered to the patient's back [15]. Petrolatum was used as a negative control. The first was after removal of the patch test on the second day (48 h), and the second was to reevaluate at 72 h [16].

Drug Provocation Test

An incremental DPT-protocol was administered in our clinic. Therapeutic single and daily doses of the drug were calculated according to the patient's age and weight. The ENDA guidelines for DPTs were followed carefully [17]. The DPT involved administering the suspected drug in 3–4 divided doses every 30 min until reaching a cumulative dose of approximately the age/weight-adjusted daily dose of the drug. The test was discontinued in the event of any reaction. Administration was open and performed by a physician with full resuscitation backup. The DPT was considered positive if any objective signs or symptoms were documented. After the last dose was administered without a reaction, the patient

was kept under surveillance for at least 2 h. If there was no reaction, the patient continued to use the full daily dose of the drug calculated according to age and weight of the patient at home in 2 divided doses for 5 days.

A positive result in any of the STs or DPT was considered confirmation of hypersensitivity to the tested drug. Patients with severe anaphylaxis, SCAR, and fixed drug eruption were considered hypersensitive based on history, even without positive patch tests.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows version 22.0 statistical software package (IBM Corp., Armonk, NY, USA). Numbers and percentages were reported for discrete variables; continuous variables were expressed as mean and standard deviation for data with normal distribution and as median and interquartile range (IQR) for non-normally distributed data. χ^2 test was used to compare nonparametric data; Mann-Whitney U test was used in comparisons with non-normally distributed continuous data and independent-samples *t* test for normally distributed continuous data. Logistic regression analysis was performed to identify factors associated with confirmed diagnosis of cephalosporin HR. *p* value <0.05 was considered statistically significant.

Results

This study included 120 pediatric patients evaluated for cephalosporin HR. The median age was 38.63 (IQR 10.5–85.7) months, and 69 (57.5%) were girls. Reactions occurring within 1 h of drug intake were reported in 33 patients (27.5%) and later than 1 h in 87 patients (72.5%). The characteristics of the patients included in this study are given in Table 1.

The median time of the drug reaction was 2 days (IQR: 1–3 days). Reactions were maculopapular rash in 55 (45.8%) patients, urticaria and/or angioedema in 49 (40.8%), anaphylaxis in 11 (9.2%), SCAR in 4 (3.3%), and fixed drug reaction in 1 patient (0.83%) (Table 1). Of 120 reactions, the most frequently reported suspected agents were cefixime in 41 patients (34.2%) and cefuroxime in 26 patients (21.7%) (Table 1).

Ninety-nine patients (82.5%) had a history of reaction to oral preparations. Of these, 82 patients (82.8%) had a history of nonimmediate reaction, 94 patients (94.9%) had only mild cutaneous involvement, 1 patient had Stevens-Johnson syndrome (SJS), 1 patient had DRESS, 2 patients had anaphylaxis, and 1 patient had fixed drug eruption. Twelve (12.1%) of the patients who had history with oral preparation were diagnosed as having cephalosporin hypersensitivity.

In 21 cases (17.5%), the suspected drug was taken by parenteral route and 9 (42.9%) of these patients had ana-

Table 1. The characterization of the patients in the study

	Reactions in 1 h after drug administration, <i>n</i> : 33/27.5%	Reactions after 1 h after drug administration, <i>n</i> : 87/72.5%	Total, <i>n</i> : 120/%
<i>Reaction type, n (%)</i>			
MPE	6 (18.2)	49 (56.3)	55 (45.8)
Urticaria	9 (27.3)	20 (22.98)	29 (24.2)
Anaphylaxis	10 (30.3)	1 (1.15)	11 (9.2)
Urticaria and angioedema	8 (24.2)	10 (11.5)	18 (15)
Angioedema	0	2 (2.3)	2 (1.7)
DRESS	0	2 (2.3)	2 (1.7)
SJS	0	1 (1.15)	1 (0.83)
Fix drug eruption	0	1 (1.15)	1 (0.83)
AGEP	0	1 (1.15)	1 (0.83)
<i>Suspicious agent route, n (%)</i>			
Oral	17 (51.5)	82 (94.3)	99 (82.5)
Parenteral	16 (48.5)	5 (5.7)	21 (17.5)
<i>Suspicious agent, n (%)</i>			
Cefixime	6 (18.2)	35 (40.2)	41 (34.17)
Ceftriaxone	14 (42.4)	4 (4.6)	18 (15)
Cefuroxime	6 (18.2)	20 (23)	26 (21.7)
Cefdinir	3 (9.1)	17 (19.5)	20 (16.7)
Cefprozil	2 (6.1)	7 (8)	9 (7.5)
Cefotaxime	2 (6.1)	1 (1.15)	3 (2.5)
Cefaclor	0	2 (2.3)	2 (1.7)
Cefpodoxime	0	1 (1.15)	1 (0.83)

SJS, Stevens-Johnson syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; AGEP, acute generalized exanthematous pustulosis.

phylaxis history. The rest had history of SCAR (*n* = 2, 9.5%) or mild cutaneous involvement (*n* = 10, 47.6%). Eighteen patients in this group had reaction history with ceftriaxone and reported reactions were nonimmediate in 4 patients (22.2%) and immediate in 14 (77.8%). Fifteen (83.3%) of the 18 patients who had a reaction history with ceftriaxone were diagnosed as hypersensitive. In total, 18 (85.7%) of the patients who had reported reactions with parenteral preparations were diagnosed as having cephalosporin hypersensitivity.

There were 11 patients with reported anaphylaxis and 9 (81.8%) of them had reactions with parenteral preparations. Three patients had positive DPT with phenoxymethyl penicillin. Eight of the patients with anaphylaxis history underwent STs and 7 had positive results. One of the patients with negative SPT and IDT had positive DPT with the suspected drug.

In the nonimmediate HR group, there were SCARs (DRESS in 2 patients, SJS in 1 patient, and acute general-

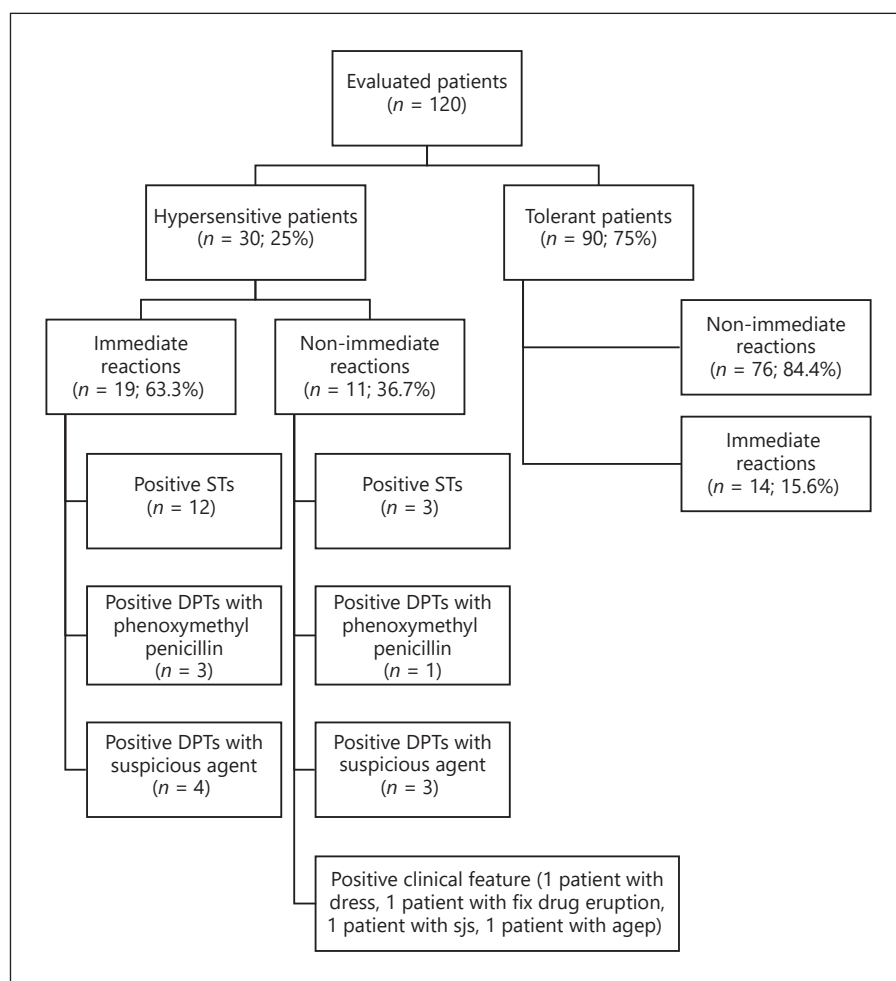


Fig. 1. The results of the diagnostic procedures. ST, skin test; DPT, drug provocation test.

ized exanthematous pustulosis in 1 patient) in 4 patients and fixed drug reaction in 1 patient. All of these patients underwent PTs, and 1 patient with DRESS had positive PT result with cefotaxime. The remaining 4 patients were diagnosed with cephalosporin HR based on clinical features.

In our study, 2 patients had positive ST results in 20 patients who were tested with classical penicillin determinants. Thirteen patients had positive ST results in 24 patients who were tested with suspicious agent. DPTs with suspicious agent were performed on 97 patients and 7 of them had reactions during the DPTs. DPTs with phenoxymethyl penicillin and/or amoxicillin-clavulanate were performed on 20 patients and 4 of them had positive result.

Cephalosporin allergy diagnosis was confirmed by ST in 15 patients and DPT in 11 and 4 patients (3 SCAR and 1 fixed drug reaction) were accepted as hypersensitive based on their clinical features (Fig. 1). In total, 25% ($n = 30$) of

the patients were diagnosed as having cephalosporin hypersensitivity from diagnostic tests and/or history. In the diagnosed group, 20 patients could be evaluated for cross-reactivity with BL ring. Six of these patients were diagnosed as cross-reactive (30%). Four of these patients were diagnosed as cross-reactive with penicillin due to positive DPT result with phenoxymethyl penicillin and 2 patients due to positive ST results with classical penicillin determinants.

Comparison of the rates of diagnostic confirmation of cephalosporin hypersensitivity between the patient groups showed that the confirmation rate was significantly lower among patients with mild cutaneous symptoms. Diagnosis of cephalosporin HR was confirmed in only 14 (13.5%) of the 104 patients who had maculopapular rash, urticarial, and/or angioedema symptoms. Confirmation of HRs was significantly more common among patients who had taken the drug parenterally ($p: 0.000$). In addition, patients with confirmed diagnoses were significant-

Table 2. Predictors of cephalosporin hypersensitivity diagnosis with skin and oral provocation tests

Parameters	Univariate			Multivariate		
	odds ratio	95% confidence interval	<i>p</i> value	odds ratio	95% confidence interval	<i>p</i> value
Immediate reaction	9.37	3.677–23.911	0.000			
Maculopapular exanthema	0.023	0.003–0.176	0.000	0.056	0.007–0.450	0.007
Urticaria/angioedema	1.147	0.497–2.647	0.748			
Parenteral drug administration	43.500	11.130–170.019	0.000	18.000	4.439–72.981	0.000

ly older than those who were drug tolerant (median age of 80.54 vs. 26.51 months; p : 0.000). Confirmation of HRs was also significantly more frequent in patients with immediate reactions (19/33 patients, 57.58%) than those with nonimmediate reactions (11/87 patients, 12.60%) (p : 0.000).

In univariate logistic regression analysis, having immediate reactions and history of parenteral intake of the suspected drug were associated with confirmed diagnosis. Maculopapular exanthema was associated with tolerance in both univariate and multivariate analyses. In the multivariate logistic regression model, parenteral intake of the suspected drug was the only significant determinant of confirmation of cephalosporin HR (Table 2).

Discussion

In our study, 120 patients were assessed for cephalosporin hypersensitivity using a combination of clinical features, STs, and DPTs, and the diagnosis of cephalosporin HR was confirmed in 25% of the patients. While the confirmation rate among patients with immediate reactions was 57.58%, this rate was only 12.60% among patients with nonimmediate reactions. The confirmation rate was especially low among patients who had skin reactions only (13.5%). In the multivariate logistic regression model, parenteral intake of the suspected drug was the only significant determinant of confirmed cephalosporin HR.

In a study of 1,431 children evaluated for BL allergy, 338 (21.5%) had suspicious history with third-generation cephalosporins. Immediate reactions were reported in 162 (11.3%) and nonimmediate reactions in 1,269 (88.7%) of the children. BL hypersensitivity was diagnosed in 30.86% (50/162) of the patients in the immediate group and 13.95% (177/1,296) in the nonimmediate group [18]. In another study about BL allergies, 13.64% (9/66) of pa-

tients in the immediate reaction group and 7.39% (53/717) of those in the nonimmediate group were diagnosed with BL HR, showing a 2-fold difference in confirmation rates between the groups [19]. In these study, no information was reported about the confirmation rates or clinical features specific to cephalosporins. In our study, 27.5% (33/120) of the patients had a history of immediate reaction and 72.5% (87/120) had a history of nonimmediate reaction. The diagnosis of cephalosporin hypersensitivity was confirmed in 57.58% (19/33) of the patients with immediate reactions and 12.6% (11/87) of those with nonimmediate reactions. This indicates that the confirmation rate is higher in the immediate group with cephalosporins, as with other BLs.

In the literature, cephalosporins have been reported to mostly cause skin rashes as HRs [4]. Similarly, 90.8% (109/120) of the patients in our study had cutaneous involvement, and 85% (102/120) had urticaria and/or maculopapular rash. Maculopapular or urticarial rashes are frequently seen as mild cutaneous reactions during BL antibiotic treatment for infectious diseases [20–22]. In children, maculopapular and urticarial rashes commonly occur due to infections [23]. This may cause a problem in differentiating between skin rashes associated with infections and those due to HRs. Similarly, in this study, confirmation of HRs was low among patients who had maculopapular rash, urticarial, and/or angioedema symptoms (13.5%, 14/104). In addition, in our study, the median age of patients with confirmed diagnosis was 80.54 months, compared to 26.51 months in the drug-tolerant group (p : 0.000). We attributed the lower median age of the tolerant group to the frequency of viral infections; therefore, mislabeling as antibiotic allergy may be more frequent in this age-group.

In a population-based study, the prevalence of reports/course of cephalosporin HR was reported to be 0.80% with oral preparations and 0.64% with intravenous preparations [6]. In our study, 99 patients (82.5%) had reac-

tion history with oral cephalosporins, and the diagnosis was confirmed in 12 (12.1%) of them. In contrast, of 21 patients (17.5%) who had reaction history with parenteral cephalosporins, the diagnosis was confirmed in 18 (85.7%). The confirmation rate was significantly higher among patients who received the drug parenterally. Macy and Contreras [6] also reported that according to US-based health plan data, the incidence of anaphylaxis was 5 in 901,908 with oral preparations of cephalosporins and 8 in 487,630 with parenteral preparations. In our study, 42.9% (9/21) of the patients who received the drug via parenteral route had history of anaphylaxis, while 94.9% (94/99) of patients with HR to oral preparations had only cutaneous involvement (excluding those with SCAR and fix drug eruption). These findings suggest that parenteral intake is associated with higher risk of serious reactions, while mild reactions are more common with oral preparations.

In our study, in the group that received the suspected drug by parenteral route, ceftriaxone was the most commonly suspected agent and HR was confirmed in 83.3% (15/18). In another study, 90 children were referred with a history of HR to ceftriaxone, 49 of those patients could be evaluated, and 26 (53%) of them were diagnosed as having ceftriaxone hypersensitivity [24]. Most (87.8%) of the patients in that study had immediate reactions, similar to our study (77.8%).

Cephalosporins can cause SCARs. One study reported SCARs in only 3 patients in a population of more than 900,000 patients exposed to more than 1,000,000 cephalosporins [6]. In our study, 4 patients (3.3%) had SCARs with cephalosporins (acute generalized exanthematous pustulosis in 1, SJS in 1, and DRESS in 2 patients) and 1 patient with DRESS had a positive result in a PT with the suspected agent.

For penicillin, after evaluation for self-reported hypersensitivity history, up to 99% of patients can tolerate penicillins [25–27]. There is a tendency to prescribe stronger or more broad-spectrum antibiotics when patients report an allergy to a particular agent. However, due to the high ratio of tolerant patients, clinical evaluation is essential [28]. In our study, although a substantial proportion (25%) of patients were diagnosed with cephalosporin HR, the majority were tolerant despite a reported history of HR. Identifying patients with real hypersensitivity is very important to avoid overusing antibiotics that are less effective, have more adverse effects, and are more expensive.

The limitation of our study is that it is retrospective. Patients whose tests were not completed were not included

in our study. Prospective observational studies on this subject can reveal the results more clearly. Despite this, the high number of patients whose tests were completed is one of the strengths of our study.

Cephalosporin hypersensitivity was confirmed in 25% of the patients in our study. Immediate reactions and parenteral intake were associated with confirmed cephalosporin HR. Although there are studies involving all BLs in children, we know of very few studies evaluating cephalosporins. More information is needed on this issue.

Statement of Ethics

This study was approved by the Ethics Committee of Ankara City Hospital (E1-20-456). Written informed consent was obtained from the patients' legal guardians.

Conflict of Interest Statement

The authors indicate no such interest.

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Author Contributions

O.Y.T. wrote the article. I.K.C., I.T.Y., and E.C. acquisition of data or analysis and interpretation of data, and reviewed the article. M.T., B.K., and E.D.M. made substantial contributions to design, reviewed the article, and gave final approval of the version to be published.

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