

Risk Stratification as a Predictive Factor for Cephalosporin Allergy: A Case-Controlled Study

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Keywords

Cephalosporins · Predictive factors · Hypersensitivity · Risk stratification · Skin test

Abstract

Background: Compared to penicillin, cephalosporin allergies are less common in children, and their diagnostic approach is less standardized. A recent European Academy of Allergy and Clinical Immunology position paper provided a risk stratification system for patients with suspected β -lactam hypersensitivity reactions. **Objective:** This study aimed to evaluate risk stratification and predicting factors for confirmed cephalosporin hypersensitivity. **Methods:** The case-controlled study included patients with confirmed cephalosporin hypersensitivity (skin tests, $n = 53$; drug provocation, $n = 19$). For each patient, 2 age- and gender-matched control subjects were included in the study. Data were retrieved from patients' records and analyzed retrospectively. Risk stratification was performed according to the severity of index reactions, which was initially divided as high and low risk and then further divided as immediate and nonimmediate. **Results:** According to risk stratification, the patient and control groups were divided as follows: high-risk immediate

(66.7% vs. 13%, respectively), high-risk delayed (1.4% vs. 8.3%, respectively), low-risk immediate (16.7% vs. 16%, respectively), and low-risk delayed (15.3% vs. 62.9%, respectively). Immediate reactions (odds ratio [OR]: 12.1, 95% confidence interval [CI]: 9–24.8, $p < 0.001$) and high-risk reactions (OR: 7.8, 95% CI: 4.1–14.6, $p < 0.001$) were associated with confirmed cephalosporin hypersensitivity in univariate analysis. Multivariate regression analysis indicated that immediate reactions (OR: 7.5, 95% CI: 3.3–16.8, $p < 0.001$) and high-risk reactions (OR: 5.2, 95% CI: 2.1–12.9, $p < 0.001$) were significant risk factors for the prediction of cephalosporin hypersensitivity. **Conclusion:** This model can be applied in children with suspected cephalosporin allergy. Skin testing provides diagnostic information in high-risk patients with immediate reactions and reduces the need for drug provocation testing in these patients. It is highly likely to confirm the diagnosis of low-risk patients directly with provocation tests without skin tests. High-risk and immediate reactions were found to be predictive factors for confirmed cephalosporin allergy.

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Introduction

Cephalosporins are antibiotics belonging to the β -lactam class [1]. The use of cephalosporins accounts for 11.4% of outpatient therapies and has increased over time [1, 2]. The frequency of allergy is reported between 0.8 and 6.9%, and cephalosporins can cause a wide variety of hypersensitivity reactions (HRs), ranging from mild urticaria and maculopapular rash to life-threatening anaphylaxis and severe cutaneous adverse reactions [2, 3]. Culprit cephalosporins are reported as cefuroxime and ceftriaxone in the general population and cefazolin in patients undergoing surgery [1, 4, 5].

The cephalosporin molecule consists of a β -lactam ring, which is the common structure of β -lactams, a dihydrothiazine ring attached to it, and side chains (R_1 and R_2). Although potentially all these structures can be immunogenic, the R_1 side chain and the remaining β -lactam moiety are central to immunogenicity [1, 6–9]. Cephalosporins are small molecules that cannot cause an allergic reaction themselves. One of the mechanisms that make them allergenic is the formation of haptens [1].

Detailed history and physical examination are the first steps in the evaluation of cephalosporin allergy. Because the history is taken months or years after the reaction occurs in most cases, the findings usually disappear during the examination, and therefore the history and examination are not sufficient for the diagnosis of drug allergy [10, 11]. Although the history is insufficient in the diagnosis of drug allergy, it is principal in classifying reactions, risk stratification, and determination of subsequent investigations [11–13]. Skin tests (STs) and drug provocation tests (DPTs) are frequently used to confirm the diagnosis [14, 15]. Recently, a risk stratification has been proposed for β -lactam antibiotics by the European Academy of Allergy and Clinical Immunology (EAACI) in a position paper, which recommended that patients could be stratified as low risk and high risk based on the morphology and severity of the index reaction and as immediate or delayed type according to the onset of symptoms [12].

At present, to the best of our knowledge, the applicability of this risk stratification in children with HRs to cephalosporins and the predictive factors for confirmed cephalosporin allergy have not been studied. The aim of this study was to identify risk factors for proven allergy in patients presenting with a history of suspected reactions to cephalosporins.

Methods

Patients

This case-control study included 2,000 children who were admitted to the Istanbul University Istanbul Faculty of Medicine Pediatric Allergy Clinic with suspected β -lactam allergy and underwent allergic evaluation between May 2012 and May 2020. Of these, 450 children had suspicious cephalosporin allergy and 90 of these were confirmed with cephalosporin allergy. Of the 90 patients, 18 were excluded due to incomplete clinical data, and thus the remaining 72 patients were included in the study and were compared with 144 control subjects who had tolerance to cephalosporin. We matched the patients in terms of 3 variables which are important in the evaluation of drug allergy, age (± 1 year), gender, and culprit cephalosporin generation. Two control subjects were selected for 1 patient. Cephalosporin hypersensitivity was defined as clinically compatible findings and a positive response in STs and/or DPTs. Cephalosporin hypersensitivity was excluded in patients whose both allergy tests (STs and/or DPTs) were negative or did not show a reaction during re-treatment.

Data Collection

Demographic and clinical data were obtained according to the European Network for Drug Allergy (ENDA) questionnaire [13]. A detailed history including the suspected HR with the culprit drug and the spectrum and timing of the symptoms was obtained from each participant. In addition, the presence of previous drug reactions, family history of drug allergy, and concomitant chronic or atopic diseases were investigated. All data were obtained from medical recordings. Children who had complete and accurate clinical information, including identification of the culprit cephalosporin, were included in the study. Participants whose allergic evaluation for cephalosporin could not be completed due to uncontrolled asthma, severe skin reaction, and parents' refusal were excluded from the study.

Risk Stratification in β -Lactam Hypersensitivity Reaction

We classified the patients based on the EAACI position paper regarding the precise diagnosis of hypersensitivity to β -lactams [12]. Patients at high risk were defined as those who had severe reactions or might experience a more severe future reaction, and patients at low risk were defined as those who experienced relatively milder reactions or might experience no reaction or a milder one in the subsequent exposure to the drug. Reactions occurring within the first 1 h after exposure to the offending drug were considered immediate-type HR and after 6 h as delayed-type HR. Reactions occurring in 1–6 h were evaluated based on clinical findings [12].

Diagnostic Evaluation

Allergic assessments were performed at the earliest 4 weeks after the suspected reactions. Prior to the tests, drugs that could affect the results were discontinued as recommended. The drugs to be used for the ST were prepared fresh on the test day [12, 16, 17]. The patients were first given an ST with cephalosporin; if negative, a DPT was applied. In the presence of clinically consistent findings, a positive response to the cephalosporin STs or DPTs was considered a confirmed cephalosporin allergy. Patients with confirmed cephalosporin allergies subsequently underwent an allergic assessment with penicillin.

Table 1. Risk stratification results and clinical findings

	Patients, <i>n</i> (%) (<i>n</i> = 72)	Controls, <i>n</i> (%) (<i>n</i> = 144)	OR	95% CI	<i>p</i> value
<i>High-risk patients</i>	49 (68.1)	31 (21.5)	7.8	4.1–14.6	<0.001
Immediate reaction	48 (66.7)	19 (13.2)	13.2	6.6–26.2	<0.001
Anaphylaxis	30 (41.7)	0			<0.001
Urticaria and/or angioedema	16 (22.2)	17 (11.8)	2.1	1.0–4.5	0.045
Bronchospasm	2 (2.8)	1 (0.7)	4.0	0.4–45.8	0.258
Hypotension	0	–	–	–	–
Delayed reaction					
Severe maculopapular eruption [†]	1 (1.4)	12 (8.3)	0.1	0.02–1.2	0.043
<i>Low-risk patients</i>	23 (31.9)	113 (78.5)	0.1	0.07–0.2	<0.001
Immediate reaction	12 (16.7)	23 (16)	1.0	0.5–2.3	0.896
Local urticaria	10 (13.9)	19 (13.2)	1.3	0.2–8.2	0.888
Pruritus	2 (2.8)	3 (2.1)	1.3	0.2–8.2	0.749
Gastrointestinal symptoms	0	1 (0.7)	–	–	–
Delayed reaction	11 (15.3)	90 (62.5)	0.1	0.05–0.2	<0.001
Mild maculopapular eruption [‡]	9 (12.5)	48 (33.5)	0.3	0.1–0.6	0.001
Urticaria	2 (2.8)	30 (20.8)	0.1	0.03–0.5	<0.001
Local infiltrative reaction at the injection site	0	7 (4.9)	–	–	–
Subjective complaints [§]	0	4 (2.8)	–	–	–
Gastrointestinal symptoms	0	1 (0.7)	–	–	–

CI, confidence interval; OR, odds ratio. [§] Nonspecific findings refer to feeling unwell, or discomfort. [†] Rash with systemic involvement (such as fever or eosinophilia) lasting longer than 1 week. [‡] Rash without systemic involvement (such as fever or eosinophilia) lasting <1 week.

Cephalosporin Skin Tests

Cephalosporin STs were performed with cephalosporin with suspected allergy. In STs with cephalosporins (ceftriaxone, ceftazidime, cefotaxime, cefuroxime, and cefazolin), both prick and intradermal tests were used, with a maximum nonirritant concentration of 20 mg/mL. SPT was considered positive when the diameter of the wheal with surrounding erythema was at least 3 mm or larger than that of the negative control after 20 min [12, 16, 17]. In case of a negative SPT, intradermal tests were performed on the volar forearm. After 20 min, the intradermal test was evaluated and considered positive if the mean diameter of the bleb with surrounding erythema increased by ≥3 mm. In patients with a suspected history of anaphylaxis, STs were started at a concentration of 0.02 mg/mL and reached 20 mg/mL in gradual increments. In delayed-type reactions, STs were evaluated repeatedly after 24 and 72 h and 7 days. Histamine (10 mg/mL) was used as the positive control, and 0.9%NaCl was used as the negative control [12, 16].

Evaluation of Penicillin Allergy

In patients with confirmed cephalosporin allergy, STs with penicillin were performed. However, the tests were only performed with benzylpenicillin (also known as penicillin G) and aminopenicillin (ampicillin) since the major determinant of penicillin could not be obtained during the study. DPTs with oral penicillin V and amoxicillin were performed for those who were found to have a negative penicillin ST. Patients with uneventful use of amoxicillin or amoxicillin-clavulanic acid after a suspected reaction to cephalosporin did not undergo an allergic assessment with penicillin.

Provocation Tests

Provocation tests were performed in patients with negative drug STs. In patients whose ST was negative with ceftriaxone or cefotaxime, an oral provocation test was performed with cefpodoxime in the first step since cefpodoxime shares the same R1 side chains as ceftriaxone and cefotaxime [8]. Due to ethical concerns, it was not applied to patients with positive STs. The DPT was applied in 3 steps and on the same day in immediate reactions, while it was performed in 5 days in delayed reactions.

Statistical Analysis

Statistical analyses were conducted using SPSS 21.0 software (IBM Corp., Armonk, NY, USA; licensed to Istanbul University). Sample size was estimated using Epi Info 2000 Statcalc software (Centers for Disease Control, Atlanta, GA, USA) with a predicted exposure of 22.5% and 4.5% for controls and patients, respectively. Accordingly, the minimum sample size (*n*) was found to be 50 patients and 99 controls. To increase the statistical power of the study, we included 72 patients and 144 control subjects in the study. Normal distribution of continuous variables was assessed using the skewness-kurtosis and the Kolmogorov-Smirnov test or Shapiro-Wilk test. Pearson's χ^2 test or Fisher's exact test was used to compare categorical data. Initially, univariate regression analysis was used to describe the association of clinical risk factors and confirmed cephalosporin allergy. Subsequently, parameters that were found significant in univariate analysis were evaluated by multivariate regression analysis. Results were presented as odds ratio (OR) with 95% confidence interval (CI), and a *p* value of <0.05 was considered significant.

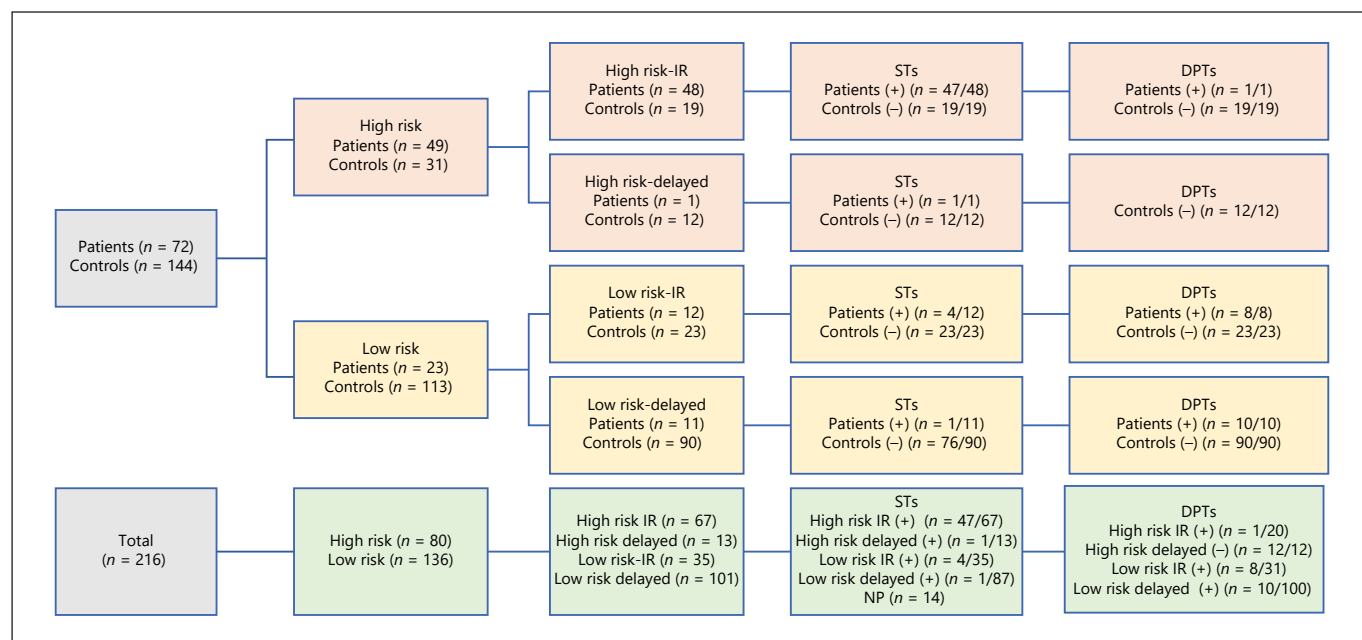


Fig. 1. Results of allergic evaluation of the children (patients and controls) with suspected reactions to cephalosporins according to the risk stratification. Cephalosporin allergy was confirmed in 53 patients with STs and 19 patients by provocation tests. Most of these patients were high-risk patients with immediate reactions

($n = 48$). Penicillin G and ampicillin STs of the patients were negative. In only 2 patients (in high-risk immediate reaction), ampicillin allergy was confirmed by oral amoxicillin/amoxicillin-clavulanate challenge. DPT, drug provocation test; IR, immediate reactions; STs, skin tests; NP, not provided.

Results

The median age was 10 (interquartile range [IQR]: 7.5–16) years in patients and 10.5 (8–16) years in controls. Median time between index reaction and allergic evaluation was 6 (IQR: 2.3–13) months in patients and 10 (IQR: 4–14) months in controls ($p = 0.057$).

Table 1 presents clinical characteristics of both groups. Of the 72 patients, 45 (62.5%) were allergic to third-generation, 26 (36.1%) to second-generation, and only 1 (0.4%) patient was allergic to first-generation cephalosporins (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000519679).

Cephalosporin hypersensitivity was confirmed by STs in 53 (73.6%) and by DPTs in 19 (26.4%) patients (Fig. 1). One patient developed anaphylaxis during the ceftriaxone skin prick test. In the control group, cephalosporin allergy was excluded by allergic evaluation (STs/DPTs, $n = 130$) or re-treatment ($n = 14$). Allergic assessment for penicillin was not performed in 4 patients since they used amoxicillin-clavulanate uneventfully after the index cephalosporin reactions. Penicillin G and ampicillin STs and oral DPTs with penicillin V were negative in 66 pa-

tients. DPT confirmed amoxicillin/amoxicillin-clavulanate allergy in 2 patients (2/72). One of these patients had anaphylaxis with cefuroxime and the other had immediate urticaria-angioedema with ceftriaxone. Penicillin allergy was excluded in all the others (70/72). Penicillin-allergic evaluation of 12 patients in the control group with a history of penicillin allergy was also negative.

In the risk stratification of the patients, there were 49 (68.1%) patients in the high-risk group, among whom 48 (66.7%) patients had immediate reactions and 1 (1.4%) patient had delayed reactions. In contrast, there were 113 (78.5%) patients in the low-risk group, among whom 23 (16%) patients had immediate reactions and 90 (62.5%) patients delayed reactions. Table 1 presents clinical findings and risk stratifications of both groups.

High-risk reactions were reported in 68.1% ($n = 49$) of the patients with cephalosporin hypersensitivity and in 21.5% ($n = 31$) of controls (OR: 7.8, 95% CI: 4.1–14.6, $p < 0.001$). In high-risk immediate reactions, this association was more apparent in patients compared to controls (66.7% vs. 13.2%; OR: 13.2, 95% CI: 6.6–26.2, $p < 0.001$). On the other hand, immediate reactions (OR: 12.1, 95% CI: 5.9–24.8, $p < 0.001$) were associated with confirmed

Table 2. Clinical characteristics

	Patients, <i>n</i> (%) (<i>n</i> = 72)	Controls, <i>n</i> (%) (<i>n</i> = 144)	OR	95% CI	<i>p</i> value
Age, median (IQR), yr	10 (7.5–16)	10.5 (8–16)			0.492
Gender-female	37 (51.4)	74 (51.4)			
Risk stratification					
High risk	49 (68.1)	31 (21.5)	7.8	4.1–14.6	<0.001
Low risk	23 (31.9)	113 (78.5)	0.1	0.01–0.2	<0.001
Chronology of the reactions					
Immediate (≤ 1 h)	60 (83.3)	42 (29.2)	12.1	5.9–24.8	<0.001
Approved penicillin class allergy					
Penicillin (amoxicillin/amoxicillin-clavulanate)	2 (2.8)	0	0.3	0.3–0.4	<0.001
Latent period [†] ≤ 1 year	47 (65.3)	89 (61.8)	1.2	0.6–2.1	0.618
Personal history of atopic disease	20 (27.8)	31 (21.5)	1.4	0.7–2.7	0.308
Concomitant chronic disease					
Cystic fibrosis	5 (6.9)	3 (2.1)	3.5	0.8–15.1	0.078
Chronic spontaneous urticarial	12 (16.7)	8 (5.6)	3.1	1.3–8.7	0.008
Having a family history of drug allergy	8 (11.1)	22 (15.3)	0.7	0.3–1.6	0.404

CI, confidence interval; OR, odds ratio. [†] Time elapsed between the last drug reaction and the current allergic evaluation.

cephalosporin hypersensitivity in univariate analysis. There was no difference between the patients and controls in terms of the rate of drug allergy assessment in the first year, presence of personal atopic diseases, and a family history of drug allergy (Table 2). When multivariate regression analysis was performed, high-risk HR (OR: 5.2, 95% CI: 2.1–12.9, $p < 0.001$) and immediate-type reactions (OR: 7.5, 95% CI: 3.3–16.8, $p < 0.001$) were found as significant risk factors for the prediction of cephalosporin hypersensitivity, while the period between the reaction and allergic evaluation was not a significant risk factor for confirmed cephalosporin allergy. Table 3 shows the risk factors for cephalosporin hypersensitivity.

Discussion

This case-control study compared the clinical findings of 72 children with confirmed cephalosporin allergies and 144 controls matched for age, gender, and cephalosporin generations. A total of 3 key confounders including the presence of reaction to >1 β -lactam antibiotic, high-risk reactions, and immediate reactions were identified. In the present study, high-risk reactions and immediate reactions were significant predictive factors for cephalosporin allergy.

The European Academy of Allergy and Clinical Immunology (EAACI) position paper reported an alternative approach based on risk stratification to be performed

in the acute stage when the allergic assessment of patients cannot be performed. Additionally, it was noted that risk stratification evaluates both the severity and chronology of the reactions and provides an algorithmic approach to determine a safe alternative β -lactam [12]. Our results showed that most of the patients in the high-risk group with immediate reactions had positive cephalosporin STs, and also sensitization with another β -lactam (penicillin) was found to be higher in these patients. Conversely, in high-risk delayed reactions, only 1 patient had a diagnosis of cephalosporin allergy confirmed by ST. These findings may provide clinical evidence that the proposed risk stratification can be used to determine patients with a high probability of having cephalosporin allergy. Accordingly, our results are compatible with previous reports [18–23].

In the present study, we had difficulty in applying risk stratification for high-risk and immediate reactions where multiple drug use and drug side effects and allergy symptoms were likely to overlap, and also for high-risk late reactions due to the similarity of infection or comorbidity and allergy symptoms [24]. We also observed that the ST results in low-risk patients with delayed reactions were not sufficient to confirm the diagnosis. Many studies have demonstrated the safety of direct oral provocations in evaluating children and adults with low-risk penicillin allergies, mostly aminopenicillins [25–28]. As suggested by the latest position paper, “especially in late maculopapular reactions in children, skin testing is not mandatory and

Table 3. Risk factors predicting cephalosporin hypersensitivity (age and gender controlled)

	B	SE	Wald	Sig	Exp (B)	95% CI for EXP (B)	
						lower	upper
Risk stratification (high risk)	1.6	0.5	12.8	<0.001	5.2	2.1	12.9
Chronology (immediate)	2.0	0.4	23.6	<0.001	7.5	3.3	16.8
Latent period <1 year*	−0.3	0.4	0.8	0.364	0.7	0.3	1.5
Constant	−0.7	0.2	15.1	<0.001	0.5		

* Time between the last suspected reaction and cephalosporin allergic evaluation.

allergic evaluation can be completed by direct provocation test in these patients” may also be valid for cephalosporins [12]. Maculopapular eruptions in children may be the result of an infection-related exanthema or drug metabolite-infection interaction rather than an immunological response to the antibiotic or may be the result of nonpermanent sensitization [24]. Moreover, recent data have also shown that even DPT-proven drug allergy (mild delayed exanthema) disappears over time [29].

Cephalosporin STs are not as standard as penicillin STs since the former has no commercial antigenic determinants and thus are performed with the parenteral form of the drugs [30, 31]. It has been shown in adult studies that patients with positive STs can tolerate these drugs [30]. Likewise, the positive predictive value of STs, particularly in children, has not been determined. In addition, ST results may vary depending on the time of conduction. Accordingly, in immediate-type reactions, sensitivity to cephalosporins in STs has been demonstrated to be lost 3–5 years after the last exposure to the drug [31]. Performing STs in the first weeks can also lead to false-negative results [12]. Despite these limitations, the cephalosporin STs are useful in the diagnosis of immediate-type reactions in children and adults, and the rates of positive responses to STs have been reported to be between 8 and 72% [14, 32, 33]. In the present study, no DPT was performed in patients with positive STs, and the rate of diagnosis with STs was remarkably higher in patients with high-risk immediate reactions, as expected. Although the STs were found negative, the diagnosis of cephalosporin allergy was confirmed in 19 patients by DPTs. These findings imply that those patients who are allergic to β -lactam antibiotics may not be allergic to the entire molecule; instead, the observed reaction may be due to the degradation products derived from disruption of the β -lactam ring or side chains.

Identifying another coexisting β -lactam sensitivity, particularly penicillin, is an integral part of cephalosporin allergy management [6, 11, 12, 34]. STs also allow to distinguish profiles of sensitization to cephalosporins. Sensitization patterns of patients with cephalosporin allergy are presented in 3 forms: cross-reactivity with penicillin, cross-reactivity with other cephalosporins (such as cefotaxime, ceftazidime, and cefuroxime), and selective reactivity to cephalosporin [34]. In addition to the unreliability of STs, in vitro tests, basophil activation test, and specific IgE measurements also make a limited contribution to the diagnosis [12]. All these barriers in the diagnosis cause the DPT to remain the gold standard in cases without contraindications. We preferred to perform the maximum single-unit dose provocation test for immediate reactions. The literature indicates that although a single dose is sufficient for immediate reactions, the duration and number of steps of DPTs in delayed reactions are controversial [12, 35–37].

In our study, allergy with aminopenicillins was confirmed in only 2 patients. Although penicillin STs (penicillin G and ampicillin) and oral penicillin V provocation tests were negative in these patients, the proof of aminopenicillin allergy by OPT suggests selective aminopenicillin allergy. Considering the cephalosporins in the history of these patients are ceftriaxone and cefuroxime, the lack of side chain similarity between these 2 cephalosporins and aminopenicillins implies the possibility of co-sensitization. Although the β -lactam core is common among aminopenicillins and cephalosporins, the tolerance of these patients to penicillin V ruled out the possibility of sensitization to the β -lactam core. Patients allergic to cephalosporins have a reaction rate of 2–30% to penicillins. This rate varies according to the antigenic structure causing sensitization and the level of similarity between the 2 β -lactam classes [38]; therefore, it is safer to advise

patients to avoid penicillins and cephalosporins until the allergic assessment is complete.

The most important limitation of this study was that it was conducted retrospectively in a single tertiary center. Therefore, it may not be representative of the general population. In addition, the evaluation of cephalosporin HR was made depending on the clinical needs of the patients, not according to the aims of the study. The diagnosis of cephalosporin allergy was made without a DPT in patients with positive STs, which may be a potential limitation in differentiating allergic sensitization from true cephalosporin allergy. On the other hand, considering that patients with positive STs are allergic to cephalosporins, we thought that it would not be ethical to perform DPTs in these patients. Finally, penicillin polylysine or benzylpeniciloyl octa-L-lysine could not be obtained during the study. However, we consider that we compensated for this limitation by performing allergic evaluation for penicillin with penicillin G and ampicillin STs and DPTs with penicillin V and/or amoxicillin and/or amoxicillin-clavulanic acid in all of these patients, and we also accepted the detection of uneventful use of penicillin in medical history as a criterion to exclude penicillin allergy.

In conclusion, the present study demonstrated that high-risk and immediate reactions are predictors of cephalosporin allergy. Further studies are needed to repeat our findings in patient groups with different sensitization patterns in different regions of the world.

References

- 1 Khan DA, Banerji A, Bernstein JA, Bilgic B, Blumenthal K, Castells M, et al. Cephalosporin allergy: current understanding and future challenges. *J Allergy Clin Immunol Pract*. 2019;7(7):2105–14.
- 2 Blumenthal KG, Wolfson AR, Li Y, Seguin CM, Phadke NA, Banerji A, et al. Allergic reactions captured by voluntary reporting. *J Patient Saf*. 2019.
- 3 Dhopeswarkar N, Sheikh A, Doan R, Topaz M, Bates DW, Blumenthal KG, et al. Drug-induced anaphylaxis documented in electronic health records. *J Allergy Clin Immunol Pract*. 2019;7(1):103–11.
- 4 Mori F, Liccioli G, Piccorossi A, Sarti L, Barni S, Giovannini M, et al. The diagnosis of ceftriaxone hypersensitivity in a paediatric population. *Int Arch Allergy Immunol*. 2019;178(3):272–6.
- 5 Lam PW, Tarighi P, Elligsen M, Nathens AB, Riegert D, Tarshis J, et al. Impact of the allergy clarification for cefazolin evidence-based prescribing tool on receipt of preferred perioperative prophylaxis: an interrupted time series study. *Clin Infect Dis*. 2020;71(11):2955–7.
- 6 Caruso C, Valluzzi RL, Colantuono S, Gaeta F, Romano A. β -Lactam allergy and cross-reactivity: a clinician's guide to selecting an alternative antibiotic. *J Asthma Allergy*. 2021;14:31–46.
- 7 Chaudhry SB, Veve MP, Wagner JL. Cephalosporins: a focus on side chains and β -lactam cross-reactivity. *Pharmacy*. 2019;7(3):103.
- 8 Zagursky RJ, Pichichero ME. Cross-reactivity in β -Lactam allergy. *J Allergy Clin Immunol Pract*. 2018;6(1):72–81.e1.
- 9 Van Gasse AL, Ebo DG, Faber MA, Elst J, Hagendorens MM, Bridts CH, et al. Cross-reactivity in IgE-mediated allergy to cefuroxime: focus on the R1 side chain. *J Allergy Clin Immunol Pract*. 2020;8(3):1094–6.e1.
- 10 Gomes ER, Brockow K, Kuyucu S, Saretta F, Mori F, Blanca-Lopez N, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug allergy interest group. *Allergy*. 2016;71(2):149–61.
- 11 Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. *J Allergy Clin Immunol Pract*. 2020 Oct;8(9S):S16–116.
- 12 Romano A, Atanaskovic-Markovic M, Barbaud A, Bircher AJ, Brockow K, Caubet JC, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams: an EAACI position paper. *Allergy*. 2020;75(6):1300–15.
- 13 Brockow K, Ardern-Jones MR, Mockenhaupt M, Aberer W, Barbaud A, Caubet JC, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. *Allergy*. 2019;74(1):14–27.
- 14 Stone CA Jr, Trubiano JA, Phillips EJ. Testing strategies and predictors for evaluating immediate and delayed reactions to cephalosporins. *J Allergy Clin Immunol Pract*. 2021;9(1):435–e13.

Statement of Ethics

The Ethics Committee of Istanbul University, Istanbul Faculty of Medicine, approved the study protocol (No. 2020/1325). Written informed consent was taken from parents and/or patients before allergic workups.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.S., N.G., and S.T. conceived and designed the study, analyzed and interpreted the data, and drafted and revised the manuscript. All authors confirm that they have reviewed and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

- 15 Yang MS, Kang DY, Seo B, Park HJ, Park SY, Kim MY, et al. Incidence of cephalosporin-induced anaphylaxis and clinical efficacy of screening intradermal tests with cephalosporins: a large multicenter retrospective cohort study. *Allergy*. 2018;73(9):1833–41.
- 16 Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs: an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2013;68(6):702–12.
- 17 Brockow K, Romano A. Skin tests in the diagnosis of drug hypersensitivity reactions. *Curr Pharm Des*. 2008;14(27):2778–91.
- 18 Chiriac AM, Wang Y, Schrijvers R, Bousquet PJ, Mura T, Molinari N, et al. Designing predictive models for beta-lactam allergy using the drug allergy and hypersensitivity database. *J Allergy Clin Immunol Pract*. 2018;6(1):139–48.e2.
- 19 Maguire M, Hayes BD, Fuh L, Elshaboury R, Gandhi RG, Bor S, et al. Beta-lactam antibiotic test doses in the emergency department. *World Allergy Organ J*. 2020;13(1):100093.
- 20 Roberts H, Soller L, Ng K, Chan ES, Roberts A, Kang K, et al. First pediatric electronic algorithm to stratify risk of penicillin allergy. *Allergy Asthma Clin Immunol*. 2020;16(1):103.
- 21 Mohamed OE, Beck S, Huissoon A, Melchior C, Heslegrave J, Baretto R, et al. A retrospective critical analysis and risk stratification of penicillin allergy delabeling in a UK specialist regional allergy service. *J Allergy Clin Immunol Pract*. 2019;7(1):251–8.
- 22 Garvey LH, Savic LC. Drug provocation testing: risk stratification is key. *Curr Opin Allergy Clin Immunol*. 2019;19(4):266–71.
- 23 Sabato V, Gaeta F, Valluzzi RL, Van Gasse A, Ebo DG, Romano A. Urticaria: the 1-1-1 criterion for optimized risk stratification in β -lactam allergy delabeling. *J Allergy Clin Immunol Pract*. 2021;S2213–2198(21):00664–4.
- 24 Vyles D, Macy E. Self-reported beta-lactam intolerance: not a class effect, dangerous to patients, and rarely allergy. *Expert Rev Anti Infect Ther*. 2019;17(6):429–35.
- 25 Labrosse R, Paradis L, Samaan K, Lacombe-Barrios J, Paradis J, Bégin P, et al. Sensitivity and specificity of double-blinded penicillin skin testing in relation to oral provocation with amoxicillin in children. *Allergy Asthma Clin Immunol*. 2020;16:57.
- 26 Pouessel G, Winter N, Lejeune S, Thumerelle C, Deschildre A. Oral challenge without skin testing in children with suspected non-severe betalactam hypersensitivity. *Pediatr Allergy Immunol*. 2019;30:488–90.
- 27 Kuruvilla M, Shih J, Patel K, Scanlon N. Direct oral amoxicillin challenge without preliminary skin testing in adult patients with allergy and at low risk with reported penicillin allergy. *Allergy Asthma Proc*. 2019;40:57–61.
- 28 Mustafa SS, Conn K, Ramsey A. Comparing direct challenge to penicillin skin testing for the outpatient evaluation of penicillin allergy: a randomized controlled trial. *J Allergy Clin Immunol Pract*. 2019 Sep–Oct;7(7):2163–70.
- 29 Tonson la Tour A, Michelet M, Eigenmann PA, Caubet JC. Natural history of benign non-immediate allergy to beta-lactams in children: a prospective study in retreated patients after a positive and a negative provocation test. *J Allergy Clin Immunol Pract*. 2018;6:1321–6.
- 30 Yuson C, Kumar K, Le A, Ahmadi A, Banovic T, Heddle R, et al. Immediate cephalosporin allergy. *Intern Med J*. 2019;49(8):985–93.
- 31 Romano A, Gaeta F, Valluzzi RL, Zaffiro A, Caruso C, Quarantino D. Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins. *Allergy*. 2014;69(6):806–9.
- 32 Romano A, Gaeta F, Valluzzi RL, Alonzi C, Viola M, Bousquet PJ. Diagnosing hypersensitivity reactions to cephalosporins in children. *Pediatrics*. 2008;122(3):521–7.
- 33 Touati N, Cardoso B, Delpuech M, Bazire R, El Kara N, Ouali D, et al. Cephalosporin hypersensitivity: descriptive analysis, cross-reactivity, and risk factors. *J Allergy Clin Immunol Pract*. 2021;9(5):1994–2000.e5.
- 34 Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol*. 2015;136(3):685–e3. e683.
- 35 Prieto A, Muñoz C, Bogas G, Fernández-Santamaria R, Palomares F, Mayorga C, et al. Single dose prolonged drug provocation test, without previous skin testing, is safe for diagnosing children with mild non-immediate reactions to betalactams. *Allergy*. 2021;76(8):2544–54.
- 36 Garcia Rodriguez R, Moreno Lozano L, Extremera Ortega A, Borja Segade J, Galindo Bonilla P, Gomez Torrijos E. Provocation tests in nonimmediate hypersensitivity reactions to beta-lactam antibiotics in children: are extended challenges needed? *J Allergy Clin Immunol Pract*. 2019;7:265–9.
- 37 Exius R, Gabrielli S, Abrams EM, O'Keefe A, Protudjer JLP, Lavine E, et al. Establishing amoxicillin allergy in children through direct graded oral challenge (GOC): evaluating risk factors for positive challenges, safety, and risk of cross reactivity to cephalosporins. *J Allergy Clin Immunol Pract*. 2021;S2213–2198:00791–1.21.
- 38 Picard M, Robitaille G, Karam F, Daigle JM, Bédard F, Biron É, et al. Cross-reactivity to cephalosporins and carbapenems in penicillin-allergic patients: two systematic reviews and meta-analyses. *J Allergy Clin Immunol Pract*. 2019;7(8):2722–38.e5.

Supplementary table 1. Culprit cephalosporins and results of allergic assessment

	Patients, n (%) n=72	Controls, n (%) n=144
Culprit drug		
First-generation	1	2
Cefazolin	1 (1.4)	2 (1.4)
Second-generation	26 (36.1)	52 (36.1)
Cefuroxime	26	52
Third- generation	45 (62.5)	90 (62.5)
Ceftriaxone	35	70
Cefotaxime	3	0
Ceftazidime	5	4
Cefixime*	1	1
Cefpodoxime proxetil*	1	15
Skin tests results		
Negative	19	130
Positive	53	0
Not performed due to uneventful re-treatment		14
Drug provocation tests		
Not performed due to skin tests positivity	53	
Not performed due to uneventful re-treatment		14
Positive	19	
Negative		130
Evaluation of penicillin allergy		
Skin tests and OPT (penicillin V/ amoxicillin) negative	66	
Safe use of amoxicillin or amoxicillin-clavulanate after index reaction	4	
Confirmed penicillin allergy (amoxicillin/amoxicillin-clavulanate)	2	

*Skin tests were performed with ceftriaxone.