



Safety of Cefazolin in Prophylaxis in B-Lactam Allergic Children

Betalaktam Alerjisi Olan Çocuklarda Sefazolin Profilaksisi Güvenliği

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ABSTRACT

Objective: Cefazolin is a first-generation cephalosporin, particularly effective against gram positive agents such as staphylococci and streptococci. Despite this narrow spectrum, it is important in surgical prophylaxis. In this study, we aimed to evaluate the tolerability of cefazolin in patients with confirmed β -lactam allergy.

Methods: Patients who underwent cefazolin allergic work-up due to suspected cefazolin allergy (Group 1) and children with confirmed β -lactam allergy other than cefazolin (Group 2) were included in the study as two groups. β -lactam allergy was confirmed by determining positivity of skin test and/or provocation test with culprit drug and penicillin. Cefazolin skin test was performed in all patients. The provocation test was also applied to all patients with negative skin tests.

Results: A total of 35 patients were evaluated. Eleven of them had a history of suspected allergic reactions after using cefazolin. The remaining 24 had a confirmed β -lactam allergy. Cefazolin allergy was confirmed in 3 patients. We confirmed cefazolin allergy in 1 of 11 children with suspected reactions. Two of the patients with confirmed β -lactam allergy had also cefazolin allergy and both of them had allergy to more than one β -lactam antibiotics.

Conclusion: The majority of patients with a β -lactam allergy can tolerate cefazolin. Our findings imply that children with confirmed allergy to more than β -lactam antibiotics and penicillin are also sensitive to cefazolin. Children with selective cefazolin allergy are expected to be sensitive to the side chain. A detailed history and comprehensive allergic evaluation are crucial in deciding the use of cefazolin in β -lactam-allergic patients.

Keywords: Drug allergy, beta-lactams, cross reaction, cefazolin

ÖZ

Giriş: Sefazolin, özellikle stafilokoklar ve streptokoklar gibi Gram-pozitif ajanlara karşı etkili olan birinci kuşak bir sefalosporindir. Bu dar spektruma rağmen cerrahi profilakside önemlidir. Bu çalışmada doğrulanmış β -laktam alerjisi olan hastalarda sefazolin tolere edilebilirliğini değerlendirmeyi amaçladık.

Yöntemler: Sefazolin alerjisi şüphesiyle sefazolin alerjisi tetkiki yapılan hastalar (Grup 1) ve sefazolin dışında β -laktam alerjisi olduğu doğrulanmış çocuklar (Grup 2) çalışmaya dahil edildi. Suçlu ilaç ve penisilin ile deri testi ve/veya provokasyon testi pozitifliği belirlenerek β -laktam alerjisi doğrulandı. Tüm hastalara sefazolin deri testi yapıldı. Deri testi negatif olan tüm hastalara provokasyon testi de uygulandı.

Bulgular: Toplam 35 hasta değerlendirildi. Bunlardan 11'inde sefazolin kullandıktan sonra şüpheli alerjik reaksiyon öyküsü vardı. Kalan 24'ünde doğrulanmış bir β -laktam alerjisi vardı. Üç hastada sefazolin alerjisi doğrulandı. Şüpheli reaksiyonları olan 11 çocuktan 1'inde sefazolin alerjisini doğruladık. Doğrulanmış β -laktam alerjisi olan hastalardan 2'si sefazoline de alerjikti ve her ikisinin de birden fazla β -laktam antibiyotiğe alerjisi vardı.

Sonuç: Betalaktam alerjisi olan hastaların çoğu sefazolini tolere edebilir. Bulgularımız, birden fazla β -laktam antibiyotiğe ve penisiline doğrulanmış alerjisi olan çocukların sefazoline de duyarlı olduğunu göstermektedir. Seçici sefazolin alerjisi olan çocukların yan zincire duyarlı olması beklenir. Sefazolin kullanımına karar vermede ayrıntılı bir öykü ve kapsamlı bir alerjik değerlendirme çok önemlidir.

Anahtar Sözcükler: İlaç alerjisi, beta-laktamlar, çapraz reaksiyon, sefazolin

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Introduction

Cefazolin is a first-generation cephalosporin group and a β -lactam antibiotic (1,2). Although cefazolin is not widely used in practice, it is a crucial agent in surgical prophylaxis (3-5). Cefazolin is preferred especially in orthopedic interventions due to its good Gram-positive efficiency and adequate bone penetration (3,6).

Approximately 10% of parents report suspected hypersensitivity to at least one β -lactam antibiotic drug in their children, although the confirmation rate is much lower, most children who are reported to be allergic to β -lactam are actually not allergic to these drug (4). In case of β -lactam allergy, the whole group is avoided due to cross-reaction concerns (5). The natural consequence of this is that surgical prophylaxis in patients with suspected or confirmed β -lactam allergy is performed with alternative agents such as clindamycin or vancomycin instead of cefazolin. This, together with enormous economic and safety issues, leads to the patient being deprived of the first-choice agent (3,7,8).

The first step in the diagnosis of drug allergy is a detailed medical history and physical examination. However, allergy testing is often required for definitive diagnosis. The most commonly used tools for this purpose are drug skin tests and provocation tests. Drug skin tests are generally used in the first stage for allergic evaluation. However, the lack of availability of antigenic determinants of the tested drug and its reactive metabolites causing the reaction, and the lack of validation of the skin test limit the reliability of skin tests. Therefore, drug provocation tests remain the gold standard for the exclusion or confirmation of drug allergy in the absence of contraindications (9,10).

Drug allergies are not permanent and tolerance to drug allergies may develop over time. Especially, cephalosporin allergies can disappear in a shorter time and at a higher rate than penicillin allergies (11,12). In this context, the necessity of avoiding the use of cefazolin in patients with a confirmed β -lactam allergy is controversial. Adult data on this subject indicate that the majority of patients with a confirmed β -lactam allergy can tolerate cefazoline (2,13,14). There is limited data on the use of cefazolin in pediatric patients with confirmed β -lactam allergy. Moreover, it may not always be possible to apply adult data to pediatric patients.

In this study, we evaluated cefazolin allergy in children based on their real-life data. Our aim was to evaluate cefazolin allergy in a group of children with history of suspected reaction to cefazolin and in children with a confirmed β -lactam allergy other than cefazolin.

Method

Study Group and Data Collection

Ethics Committee of İstanbul University approved the study protocol (no: 2020/1325). Informed consents were obtained from the patients and/or their parents. This study was performed according to the regulations of the Declaration of Helsinki.

In the study, children who were admitted to İstanbul University İstanbul Medical Faculty Pediatric Allergy and Immunology Department between May 2017 and May 2021 with suspected cefazolin reaction or confirmed β -lactam allergy other than cefazolin were evaluated.

Patients who underwent cefazolin allergic work-up due to suspected cefazolin allergy (Group 1) and children with confirmed β -lactam allergy other than cefazolin (Group 2) were included in the study as two groups. Patients whose allergic evaluation for cefazolin could not be completed due to uncontrolled asthma, severe skin reaction, and parents' disapproval, and patients with suspected delayed reactions were excluded from the study.

Demographic and clinical data of the patients were recorded according to the European Network for Drug Allergy (ENDA) questionnaire (15). Detailed history regarding the culprit drug, spectrum and timing of the symptoms, previous drug reactions and family history of drug allergy, presence of underlying chronic diseases or atopic diseases were obtained from the family and the patients' medical recordings. Informed consent was obtained from the patients and/or their families in the study.

Reactions that were thought to be clinically mediated by immunoglobulin E, such as urticaria, angioedema or anaphylaxis, occurring within six hours were accepted as immediate-type reactions (10).

Diagnostic Evaluation

Tests were performed at the earliest 4 weeks after the suspected reaction. Before the tests were carried out, medications that could affect the results were discontinued as recommended in an appropriate time (9,15,16). The tests with suspected β -lactams were done with one-week intervals.

In patients with confirmed β -lactam allergy, allergic evaluation was performed with the culprit β -lactam and penicillin. Since major determinant of penicillin could not be obtained for all patients, we were only able to perform penicillin skin tests with benzyl penicillin (penicillin G) and aminopenicillin (ampicillin) in patients with suspected β -lactam allergy. Skin tests were performed with recommended concentrations (10,15).

Skin prick test (SPT) with cefazolin was performed to each subject at full-strength concentrations of the drug (20 mg/mL). SPT was considered as positive when the wheal diameter was at least 3 mm or larger than the negative control with surrounding erythema after 20 minutes. In case of a negative SPT, intradermal tests (IDTs) were performed on the volar forearm skin at 2 mg/mL and 20 mg/mL concentrations, as recommended by ENDA, respectively on volar forearm skin. After 20 minutes, IDT was evaluated and considered as positive if the mean diameter of the bleb increased by 3 mm or more with surrounding erythema. Histamine at 10 mg/mL concentrations was used as positive control and 0.9% NaCl was used as negative control as recommended by ENDA (9,10).

If skin tests were negative, the patient was invited subsequently for a drug provocation test (DPT). These tests were performed

only in patients with negative skin tests, and not in patients with positive skin tests due to ethical concerns. Drug provocation tests were carried out in hospital setting in accordance with ENDA recommendations (10). The provocation test was accepted as positive in those who had skin findings, respiratory, cardiovascular or gastrointestinal system findings, or changes in vital signs during or after the test (9,10).

Cefazolin provocation tests were performed in two steps via intravenous route at hospital setting, with a total dose of 50 mg/kg. It was started with 1:10 of the single dose, followed by the remainder after 30 minutes.

Anaphylaxis was diagnosed according to the presence of the clinical criteria (17).

In the presence of compatible history, a positive skin test and/or a provocation test against a β -lactam antibiotic was accepted as β -lactam allergy. If drug skin and provocation tests were negative, drug allergy was excluded.

Statistical Analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) program (Version 23.0. Armonk, NY.). Pearson chi-square test or Fisher’s Exact test was used to compare the categorized data. The normality of the distribution of continuous variables was evaluated with the skewness-kurtosis and the Kolmogorov-Smirnov test or Shapiro-Wilks test. Those which did not show normal distribution among continuous variables were given as median and interquartile range (IQR). Nonparametric tests (Mann-Whitney U or Kruskal-Wallis) were used to compare data that did not show normal distribution. A value of $p < 0.05$ was accepted to be statistically significant.

Results

Thirty-five children were evaluated for cefazolin allergy. Eleven of the patients (31.4%) in the study group reported suspected

allergic reactions after using cefazolin (Group 1). The remaining 24 patients had at least one confirmed β -lactam allergy other than cefazolin and those patients had never used cefazolin (Group 2). Clinical characteristic of the patients in each group are summarized in Table 1.

Cefazolin allergy was detected by using skin tests in 8.5% of the patients (n=3) and it was excluded by using DPT in the remaining of patients (n=31). We found that 9.1% (1/11) of those with suspected cefazolin allergy (Group 1), and 8.3% (2/24) of patients with confirmed β -lactam allergy had allergy to cefazolin (Group 2). The diagnostic approach for cefazolin allergy is demonstrated in Figure 1.

We found that 2 patients were sensitive to both cefazolin and other β -lactams. One of these patients was allergic to ceftriaxone and meropenem in addition to cefazolin, and the other to cefuroxime and amoxicillin-clavulanate (Figure 1). Those two patients were also found to be allergic to penicillin by using skin test and/or drug provocation tests. Cefazolin provocation tests were found negative in all patients with negative skin tests.

Within the group of children with confirmed β -lactam allergy, the presence of cefazolin allergy was found to be significantly higher in patients allergic to more than one β -lactam antibiotics ($p=0.015$). Comparison of the clinical features of the patients allergic or tolerant to cefazolin is presented in Table 2. We found that confirmed allergy to more than one β -lactam group was a risk factor for cefazolin allergy ($p=0.009$, 95% confidence interval: 2.7-1402). Characteristics of patients with confirmed cefazolin allergy are illustrated in Table 3.

Discussion

In our study, we found that the vast majority of patients with confirmed β -lactam allergy were tolerant to cefazolin. The only significant risk factor for cefazolin allergy was the presence of confirmed allergy to more than one β -lactam antibiotics.

Table 1. Clinical features and diagnostic results of the patients

	Confirmed β -lactam allergy other than cefazolin n=24	Suspected history of cefazolin allergy n=11	p
Age median (IQR) years	11 (5.2-15)	10 (7.5-11.5)	0.713
Having atopic disease	10 (41.7)	1 (9.1)	0.054
Asthma (\pm allergic rhinitis)	9	1	
Atopic dermatitis with food allergy	1	0	
Family history of a drug allergy	7 (29.2)	0	0.045*
Clinical presentations			
Anaphylaxis	9 (37.5)	1 (9.1)	0.084
Urticaria-angioedema	15 (62.5)	8 (72.7)	0.554
Nonspecific finding	0	2 (18.2)	0.092*
Diagnostic results of cefazolin allergy			
Confirmed	2 (8.3)	1 (9.1)	1*
Excluded	22 (91.7)	10 (90.9)	

*Fisher exact test was applied.
IQR: Interquartile range

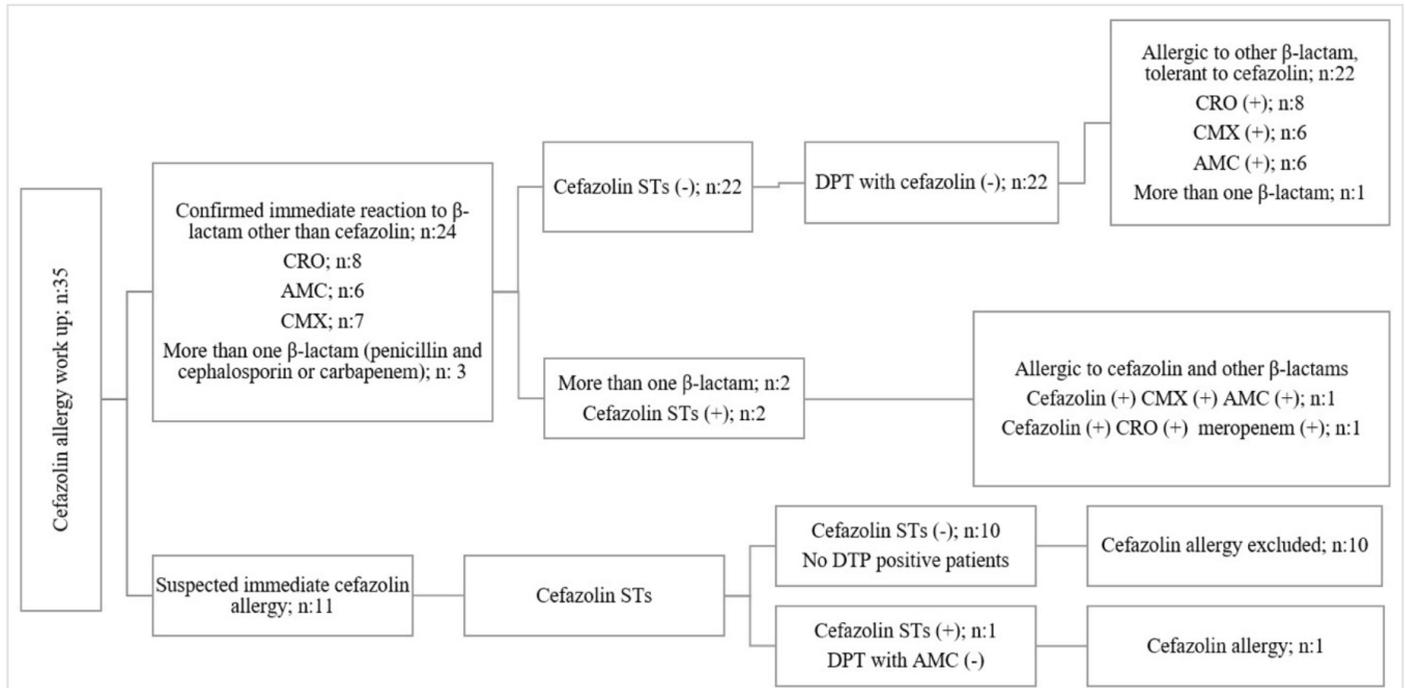


Figure 1. Allergic evaluation results for cefazolin and other β-lactams. Drug allergy diagnosis was confirmed by determining positive response in skin test and / or provocation test. Allergic evaluation for cefazolin was performed in 35 patients. Cefazolin allergy was confirmed in 2 of 24 patients allergic to multiple β-beta lactam antibiotics including penicillin. Cefazolin allergy was confirmed in only 1 of 11 patients who reported suspected allergies to this drug.

AMC: Amoxicillin-clavulanate, CRO:Ceftriaxone, CMX: Cefuroxime, DPT: Drug provocation test, STs: Skin tests

Table 2. Comparison of the clinical features of the patients allergic-and tolerant to cefazolin

	Allergic n=3 (8.5)	Tolerant n=32 (91.5)	p
Age, median (IQR) years	12 (12.5-14)	9 (5-13.5)	0.140
Gender-male	2 (66.7)	17 (53.1)	0.603*
Time between a confirmed β-lactam or suspected cefazolin allergy and diagnostic work-up for cefazolin, median (IQR) months	26 (13.5-34)	12 (9-24)	0.714
Confirmed allergy with more than one β-lactam group, including penicillin	2 (66.7)	1 (3.1)	0.015*
Cefazolin allergic work-up indication			
Group 1 (suspected with cefazolin allergy)	1(33.3)	10 (31.3)	1*
Group 2 (confirmed with β-lactam allergy except cefazolin)	2 (66.7)	22 (68.8)	
Clinical presentation of β-lactam allergy			
Anaphylaxis	3 (100)	7 (21.9)	0.018*

*Fisher exact test was applied.
IQR: Interquartile range

Since cefazolin is a β-lactam group antibiotic, its use in patients with confirmed β-lactam allergy may cause the risk of cross-reactions. The safety of cefazolin usage in patients with β-lactam allergy is related to the β-lactam sensitivity pattern. If there is sensitization to common structures, such as β-lactam core, it should be avoided (5,18).

Sensitization patterns of the patients with cefazolin are presented in tree forms; cross-reactivity with penicillin, selective reactivity to cefazolin or cross-reactivity with another cephalosporin

(ceftazole) (5,13,18). Cefazolin, which is the most common cephalosporin to cause anaphylaxis in some countries, has unique R₁ and R₂ side-chain groups and does not appear to cross-react with other cephalosporins except ceftazole, a first-generation agent that is only available in some countries. Several studies suggest that skin test positive patients with past immediate reactions to cefazolin often tolerate most of the cephalosporins and other β-lactams (2,13,14,19). In our study, two of the patients with confirmed multiple β-lactam allergy were sensitive to cefazolin. Although the number of our patients with sensitivity

Table 3. Clinical characteristics of patients with confirmed cefazolin allergy

Patient number	Age & gender	Culprit drug	Clinical presentation	Time elapsed, months	Drug skin tests results				DPT results			Confirmed β-lactam*	Possible sensitization pattern
					Penicillins STs	Cephalosporins STs	Carbapenems STs	PV	AM/AMC	Cefazolin	Carbapenems STs		
Patient with confirmed β-lactam allergy, other than cefazolin													
1	12-F	CRO, meropenem	A	26	+	+	CRO +	+ ^s	NP	NP	NP	CRO + meropenem, AMP	B-lactam core
2	16-M	AMC-AMP-s, CMX,	A	42	+	+	CMX+	NP	NP	+	NP	CXM+AMC	B-lactam core
Patient with suspected cefazolin allergy													
3	13-F	Cefazolin	A	1	-	-	NP	NP	-	-	NP	No confirmed beta-lactams	Side chain

A: Anaphylaxis, AM: Amoxicillin, AMC: Amoxicillin-clavulanic, AMP - S: Ampicillin-sulbactam, CRO: Ceftriaxone, CXM: Cefuroxime, DPT: Drug provocation test, F: Female, M: male, NP: Not performed, PG: Penicillin G, PV: Penicillin V STs; Skin tests

to cefazolin was low, this finding implied that multiple β-lactam allergy might be a risk factor for cefazolin allergy. Based on the fact that β-lactam allergy is the most common drug allergy in children, (4) the risk of cross-reactions with other β-lactams may raise concerns for cefazolin use (5,20-22). Of our two patients with cefazolin allergy; patient no 1 was found to be sensitive to ceftriaxone and meropenem, and patient no 2 to cefuroxime and amoxicillin-clavulanate. This findings together with the presence of penicillin allergy in those children confirmed that the sensitivity of our two patients was to the β-lactam core. On the other hand, all children with confirmed allergy to a β-lactam were tolerant to cefazolin. This could be explained by the sensitivity to the side chains. Similarly, we believed that patient no 3 was sensitive to cefazolin side chains, because he had sensitivity only to cefazolin in the skin test with negative results for penicillin allergy evaluation. The β-lactam sensitivity pattern is directly related to the habit of prescribing a drug in the population (23). In β-lactams frequently used such as amoxicillin-clavulanic acid and cefuroxime or ceftriaxone, sensitivity to the side chains is mostly found (5,23,24). Our results seem to be consistent with the literature for these drugs.

Considering that history of drug reactions are mostly not true and it may disappear over the time even if it is real, (25) it is not appropriate for these patients to avoid cefazolin, which is the first choice especially in surgical prophylaxis. Avoiding this agent and using alternative drugs such as vancomycin or clindamycin is important in terms of increased resistant bacteria in surgical infections (5-8). It is indisputable that this practice mentioned above may cause health and economic problems.

There are some difficulties in confirming the diagnosis of a patient with suspected cefazolin allergy in determining the sensitivity pattern. We could not use benzylpenicilloyl octa-L-lysine and penicillin G at the same time (26). In addition, there are no commercially available reagents for cephalosporin skin tests and therefore tests are usually done with parenteral form of the culprit cephalosporin (12,18,19,24,27). We thought that we overcame the difficulties encountered in diagnosing cefazolin allergy by including only patients with immediate type reaction in our study and by performing a provocation test with cefazolin in all patients with negative skin test results.

Conclusion

In conclusion, our findings showed that patients with confirmed allergy to a β-lactam antibiotic can usually tolerate cefazolin. Children with sensitivity to multiple β-lactam antibiotics and penicillin are expected to be allergic to cefazolin due to sensitivity to β-lactam core. A detailed history and comprehensive allergic assessment are essential to decide on the use of cefazolin.

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Ethics

Ethics Committee Approval: Ethics Committee of İstanbul University approved the study protocol (no: 2020/1325).

Informed Consent: Informed consents were obtained from the patients and/or their parents.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: A.S., E.Y., N.G., Design: A.S., E.Y., N.G., Data Collection or Processing: Z.T., N.G., Analysis or Interpretation: Z.T., N.G., Literature Search: A.S., E.Y., N.G., Z.T., N.G., Writing: A.S., E.Y., N.G., Z.T., N.G.

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