

## Allergic reactions to cephalosporin antibiotics in a 15-year-old population

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### Abstract

Cephalosporin, along with penicillin, are among the least harmful antibiotics. It is widely prescribed for common infections such as bronchitis, otitis media, pneumonia and cellulitis. A contraindication for this agent is a history of penicillin allergy, due to possible cross-reactions of hypersensitivity to penicillin and cephalosporin. Hypersensitivity reactions can occur in any mode of administration and to almost all antibiotics. Hypersensitivity reactions to cephalosporin are very similar to those of penicillin. The purpose of the study was to determine whether exist reactions to cephalosporin in the study population, and to determine whether exist statistically significant differences in the occurrence of allergic reactions to cephalosporin between boys and girls of the same age and whether exist differences in the occurrence of allergic reactions between subjects in urban and rural areas. The sample consisted of 1605 respondents, the sample was randomly selected and stratified by sex, and all data were processed in the statistical program. The results of the research show that 9.1% of the total population of boys and girls aged 15 from the Tuzla Canton are allergic to some type of antibiotic. The percentage of allergic reactions to cephalosporin is statistically significantly higher in the total population of 15 - year - olds from suburban and urban settlements than among peers in rural areas. Allergic reactions to cephalosporin were not observed in the group of boys from urban and suburban settlements as well as girls from rural settlements. This research also showed that there are statistically significant differences in the occurrence of cephalosporin allergies between urban and rural respondents.

**Keywords:** Cephasporin Antibiotics; Allergies; Male and Female population; Urban and Suburban areas

### 1. Introduction

Cephalosporin are a group of beta-lactam antibiotics. Cephalosporin differ from penicillin only in better penetration through the cell wall of gram-negative bacteria [1]. They are usually used as a substitute for penicillin in the treatment of infections caused by gram-negative bacteria, and in prophylaxis in surgical procedures [2]. It should be noted that cephalosporin (along with penicillin) are among the least harmful antibiotics.

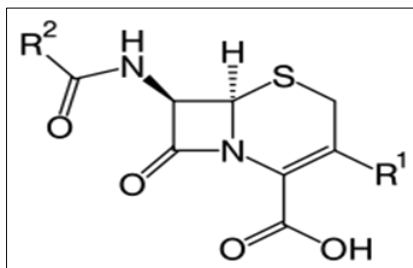
The hypersensitivity reaction is very similar to which occurs with penicillin (skin rash, serum sickness, Stephen Johnson syndrome and anaphylaxis). A cross-allergic reaction may occur. Approximately 10% of individuals sensitive to penicillin also have an allergic reaction to cephalosporin. Nephrotoxicity has been reported (especially with cefradine) and, unlike penicillin, should not be combined with aminoglycosides and furosemide (a diuretic). Diarrhea may occur with cephalosporin for oral administration.

This paper aimed to find out whether there are significant differences in the occurrence of allergic reactions to cephalosporin between boys and girls, as well as whether there are statistically significant differences between urban and rural populations.

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### 1.1. Structure of cephalosporin

All cephalosporin have a common nucleus, 7-amino-cephalosporic acid (7-ACK), which contains one dihydrothiazine and one  $\beta$ -lactam ring [3]. This nucleus is analogous to the penicillin nucleus, but insufficiently potent for clinical use. By changing the R1 and R2 radicals, we get a large number of cephalosporin antibiotics, the first of which was produced in 1964 – cephalotin.



**Figure 1** Chemical structure of the cephalosporin nucleus- (7ACK) (Graham, L.P., 1995: An Introduction to Medicinal Chemistry Department of Chemistry, Paisley University, Oxford University Press, Oxford.)

### 1.2. Mechanism and Spectrum of Action

Cephalosporin are bactericidal like other beta-lactam antibiotics, but are less susceptible to the enzyme penicillase [4]. The emergence of *E. coli* and *Klebsiella* strains, which produce extended-spectrum  $\beta$ -lactamases (ESBL), which can hydrolyze most cephalosporin, is becoming an increasing problem [5]. Cephalosporin interfere with the synthesis of peptidoglycans in the bacterial cell wall by interfering with the action of transpeptidase and irreversibly inhibiting the final transpeptidation, which interrupts the synthesis of the bacterial cell wall.

### 1.3. Pharmacokinetics

Only a few cephalosporin are stable in acidic gastric medium and can be administered orally (cephalexin, cefradine, cefadroxil, and cefaclor). Most other cephalosporin are administered parenterally or topically (i.m., i.u.), and  $C_{max}$  in plasma are achieved on average 30 minutes after administration.

Cephalosporin pass into most body tissues and fluids and are found in the kidneys, lungs, soft tissues, liver, bile, and in joints and bones. They penetrate the CST poorly during inflammation. Third-generation cephalosporin pass well into the cerebrospinal fluid. They also pass through the placenta into the fetus. They bind to plasma proteins to varying degrees. A large percentage is excreted undigested by the kidneys (most by tubular secretion, less by glomerular filtration), and some significantly by bile. The addition of probenecid may reduce renal tubular secretion, whereas ceftazidime is not blocked by probenecid because it is excreted only by glomerular filtration [6]. In any case, in case of kidney damage, the dose of cephalosporin should be reduced. Several cephalosporin (e.g., cefotaxime) are deacetylated in the liver to significantly less active metabolites.

### 1.4. Resistance

Bacteria become resistant to cephalosporin much like penicillin antibiotics. Resistance is due to the breakdown of the drug by  $\beta$ -lactamases (cephalosporinase) and they are not sensitive to penicillinase produced by gram-positive bacteria (eg *Staphylococcus aureus*). Resistance can occur due to the specific structure and impermeability of the outer layer of the cell wall for them (eg *Pseudomonas aeruginosa*), and some types of bacteria become resistant due to changes in the structure of receptors in their wall, which bind cephalosporin and penicillin (PBP - penicillin binding proteins). In general, their activity is weaker compared to penicillin, but they have a wider range of action. Their sensitivity to  $\beta$ -lactamases is different [7].

## 2. Examinees and Method

### 2.1. Sample of respondents

The sample of examinees for this research consists of a group of boys and girls, primary and secondary school students from the Tuzla Canton at the age of 15. The sample was collected from January 1, 2018 to May 30, 2019. It consists of a total of 1605 respondents, of which 574 respondents are from rural areas (226 boys and 348 girls), 665 respondents

from urban schools (357 boys and 308 girls) and 366 respondents from suburban schools (116 boys and 250 girls). The sample of respondents was divided into two groups:

- Experimental group: boys aged 15 years from the Tuzla Canton.
- Control group: 15-year-old girls from the Tuzla Canton.

## 2.2. Data collection method

Subjects were selected by random sampling. The research was conducted voluntarily. The questionnaire was submitted to schools with the previously obtained consent of the Ministry of Education and Science of Tuzla Canton (Number: 10 / 1-38-3462 / 19), and for the accuracy of the data, it was filled out by the parents or guardians of the examinees. The age of the respondents is from 14.6 to 15.5 years. The survey questionnaire consisted of several questions, such as: the exact age of the respondents, whether the antibiotic was ever used in therapy, what type of antibiotic was most often used, the length of therapy, whether there are allergies to antibiotics and which, whether antibiotics are used only with a doctor's recommendation, do they follow the instructions for use, especially when it comes to regular use and duration of therapy, do they always feel better after antibiotic therapy and what is the most common type of prescribed therapy - topical, per os or parenteral.

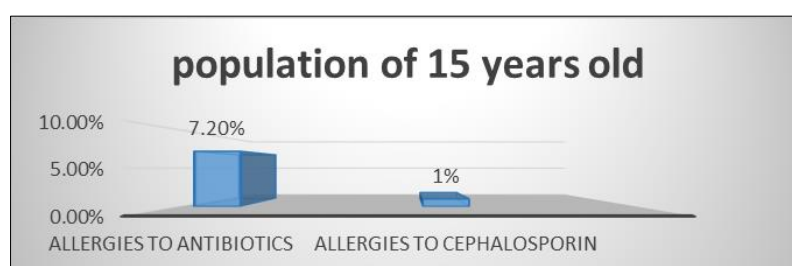
## 2.3. Data processing method

After data collection, the division into gender categories and data collection area was performed, and then for each sex certain age categories and settlements were calculated basic statistical parameters and statistical significance ( $\chi^2$ -test hi-square), between the compared categories of respondents. All data were processed in Microsoft Office Excel 2013 and SPSS 21 statistics, and presented in Microsoft Office Word 2013. The first part of statistical data processing consisted of analysis of the sample by groups, which are expressed in the form of tables and graphs. Testing of the selected data was performed by chi-square test. Significance of the association was determined by chi-square test at a significance level of 0.05. The null hypothesis can be accepted if the value of  $p > 0.05$ , ie. There is no statistically significant correlation between the tested data. Measurements were performed with a contingency coefficient (phi-coefficient) and a Cramer coefficient at the significance level of 0.05. The correlation was measured by the Pearson correlation coefficient, at the significance level of 0.05. In the end, all the obtained results are presented in tables and graphs.

## 3. Results and discussion

**Table 1** Percentage of occurrence of allergic reactions to cephalosporin in the population of 15 years of urban settlement

	Antibiotic allergies		Allergies to cephalosporin
	Yes	No	
Boys	27 (8.18%)	303 (91.8%)	0 (0.0 %)
Girls	18 (6.12%)	276 (93.9%)	6 (33.3%)
Total	45 (7.2%)	579 (92.8%)	6 (1%)



**Figure 2** Percentage of occurrence of allergic reactions to cephalosporin in the population of 15 years of urban settlement

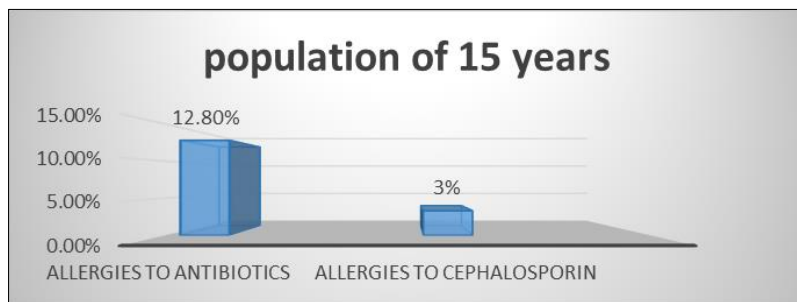
The results of the research show that 7.21% of the total population of boys and girls aged 15 from the area of the city of Tuzla is allergic to some type of antibiotic. Of these, 1% are allergic to cephalosporin. In the urban population, allergies

to cephalosporin are present only in the group of girls and make up one third of allergic reactions to antibiotics present in the female population (table 1).

**Table 2** Percentage of occurrence of allergic reactions to cephalosporin in the population of 15 years of suburban settlement

	Antibiotic allergies		Allergies to cephalosporin
	Yes	No	
Boys	20 (17.2%)	96 (82.76%)	0(0.0%)
Girls	27 (10.8%)	223 (89.2%)	12 (44.4%)
Total	47 (12.8%)	319 (87.2%)	12 (3.3%)

The percentage of allergic reactions in the total population of boys and girls aged 15 from suburban settlements is 12.8%. 3.3% of this population is allergic to cephalosporin. In this population as well, allergies to cephalosporin are present only in the group of girls, and they make up 44.4% of all allergies to antibiotics present in the female population.

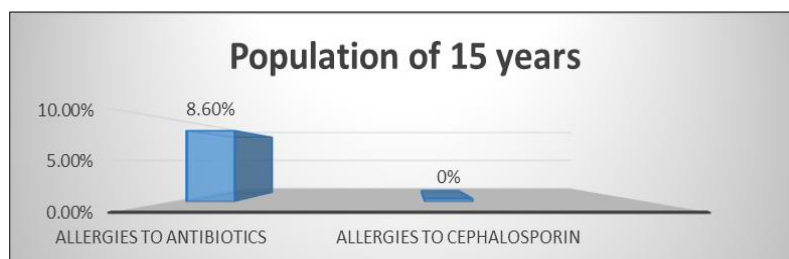


**Figure 3** Percentage of occurrence of allergic reactions to cephalosporin in the population of 15 years of suburban settlement

**Table 3** Percentage of occurrence of allergic reactions to cephalosporin in the population of 15 years of rural settlement

	Antibiotic allergies		Allergies to cephalosporin
	Yes	No	
Boys	24 (10.7%)	200 (89.3%)	2 (8.3%)
Girls	24 (7.3%)	309 (93.6%)	0(0.0%)
Total	48 (8.6%)	509 (91.4%)	2 (0.36%)

The percentage of allergic reactions to antibiotics in the population of boys and girls aged 15 years in rural areas are shown in Table 3 and Figure 4. The table shows that 8.6% of the rural population is allergic to some type of antibiotic and 0.36% are allergic to cephalosporin. In contrast to urban and suburban environments, allergies to cephalosporin were observed only in the group of boys.

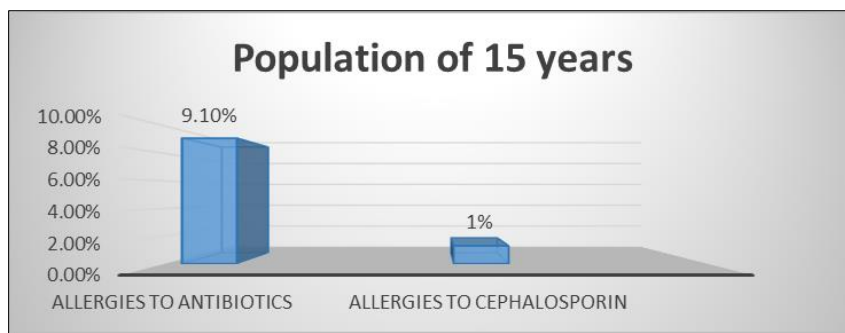


**Figure 4** Percentage of occurrence of allergic reactions to cephalosporin in the population of 15 years of rural settlement

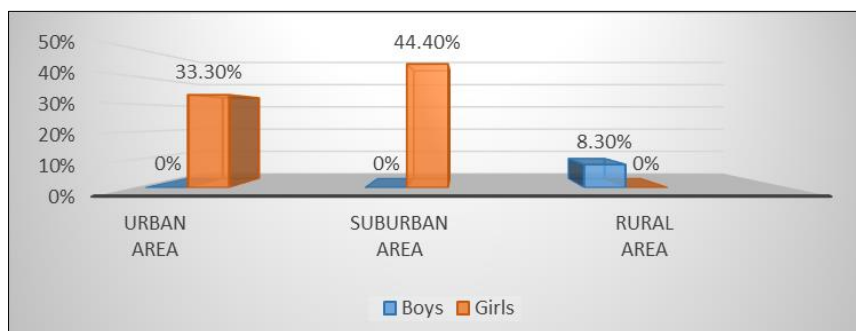
**Table 4** Percentage of occurrence of allergic reactions to certain classes of antibiotics in the total population of 15 years of Tuzla Canton

	Allergies to antibiotics		Allergies to cephalosporin
	Yes	No	
Boys	71(10.6%)	599 (89.4%)	2 (2.8%)
Girls	69 (7.9%)	805 (92.1%)	18 (26.1%)
Total	140 (9.1%)	1404 (91%)	20 (1.3%)

Table 4 shows data on the occurrence of allergic reactions in the total sample of boys and girls in Tuzla Canton. The table shows that 1.3% of the total population of 15 years in Tuzla Canton is allergic to cephalosporin. A higher percentage of cephalosporin allergies was reported in the girls group than in the boys group.



**Figure 5** Percentage of occurrence of allergic reactions to cephalosporin in the total population of 15 years of Tuzla Canton



**Figure 6** Differences in the occurrence of allergic reactions to cephalosporin between boys and girls in urban, suburban and rural areas

**Table 5** Differences in the occurrence of allergic reactions to cephalosporin between the observed groups of subjects

Compared categories	N	df	Phi value	Cramer's value	Contingency coefficient	Pearson Square	Chi-	Sig. (p)
Boys-Girls in the total sample	140	1	-0.332	0.332	0.315	15.475		0.000
City-Village	140	1	0.209	0.209	0.204	6.108		0.013

The data in Table 5 show that there are statistically significant differences in the occurrence of cephalosporin allergy between boys and girls aged 15 years, ie. Cephalosporin allergies are more present in the female than in the male

population. There are also statistically significant differences between the occurrence of allergic reactions to cephalosporin between urban and rural areas. Namely, in the urban areas, a larger number of respondents have allergies to cephalosporin compared to respondents in rural areas.

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#### 4. Conclusion

Antibiotic allergies are present in a higher percentage in suburban and rural settlements than in urban ones. The research showed that allergies to cephalosporin are present only in the group of girls in urban and suburban settlements and only in the group of boys in rural areas. It was also noted that in the total population of 15 years of Tuzla Canton, a higher percentage of allergies to cephalosporin was recorded in the group of girls. It was found that there are statistically significant differences in the occurrence of allergic reactions to cephalosporin between boys and girls, ie. Cephalosporin allergies are more present in the female than in the male population. There are also statistically significant differences between the occurrence of allergic reactions to cephalosporin between urban and rural areas. Namely, in the urban areas a larger number of respondents have allergies to cephalosporin compared to respondents in rural areas. Future research may focus on the causes and factors that cause the occurrence of different degrees of allergic reactions to antibiotics between the male and female populations. It is also possible to examine why there are differences in the occurrence of allergic reactions between the respondents of urban and rural settlements, whether it is environmental factors, lifestyle or more frequent prescribing of certain antibiotics in one of the populations.

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#### Compliance with ethical standards

##### *Acknowledgments*

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##### *Disclosure of conflict of interest*

The author declare that there is no conflict of interests regarding the publication of this paper.

##### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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