

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

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### Abstract

Macrolides are antibiotics that can be used to treat various infections. Allergic reactions to macrolides are rare, but may include minor to severe skin reactions, as well as systemic life-threatening reactions such as anaphylaxis. Hypersensitivity reactions can occur in any mode of administration and to almost all antibiotics. The purpose of the study was to determine whether there are reactions to macrolides in the study population, and to determine statistically significant differences in the occurrence of allergic reactions to macrolides between boys and girls of the same age and whether there are differences in the occurrence of allergic reactions between respondents in urban and rural areas. The sample consists 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 in the total population of 15-year-olds from suburban settlements is slightly higher than among peers in urban areas, but the differences are not statistically significant. A higher rate of allergic reactions was recorded in the group of boys from urban and rural areas. Macrolide allergies were found only in a group of boys in rural areas. This study confirmed that allergies to macrolides are rare and revealed differences in the occurrence of allergic reactions between girls and boys.

**Keywords:** Macrolide Antibiotics; Allergies; Male and Female population; Urban and suburban areas

### 1. Introduction

Drugs as foreign substances to the body, in addition to the pharmacological effect, can also cause side effects. These adverse drug reactions are divided into two basic groups - type A and type B. The most common are type A reactions (80%) and can occur in any person. They occur due to toxic or other pharmacologically expected effects such as overdose, side effects, accumulation and interactions. Type B reactions occur in 20% of cases and are not related to the pharmacological action of the drug. These reactions include allergies (hypersensitivity) to the drug, and their development involves immune mechanisms, and non-immune hypersensitivity, which includes pseudoallergic reactions, reactions related to changes in metabolism or enzyme deficiency, and intolerance to drugs [1,2].

Allergic reactions mediated by IgE antibodies usually occur from a few minutes to a few hours after drug administration (depending on the route of administration). If the reaction occurs within one hour of drug administration (regardless of the route of administration), there is a significantly higher risk of anaphylaxis when re-administering the same drug [3]. Reactions that are not mediated by IgE antibodies most often manifest after 6 hours of drug administration (delayed reactions) or a few days after discontinuation of the drug, e.g. ampicillin allergy most often manifests itself after 7–10 days from the start of treatment, and often 1–3 days after the end of treatment [4].

However, hypersensitivity reactions caused by macrolides use are rare (0.4-3%) [5]. Hypersensitivity reactions are rare but gastrointestinal disorders are common after oral administration (nausea, diarrhea and abdominal pain).

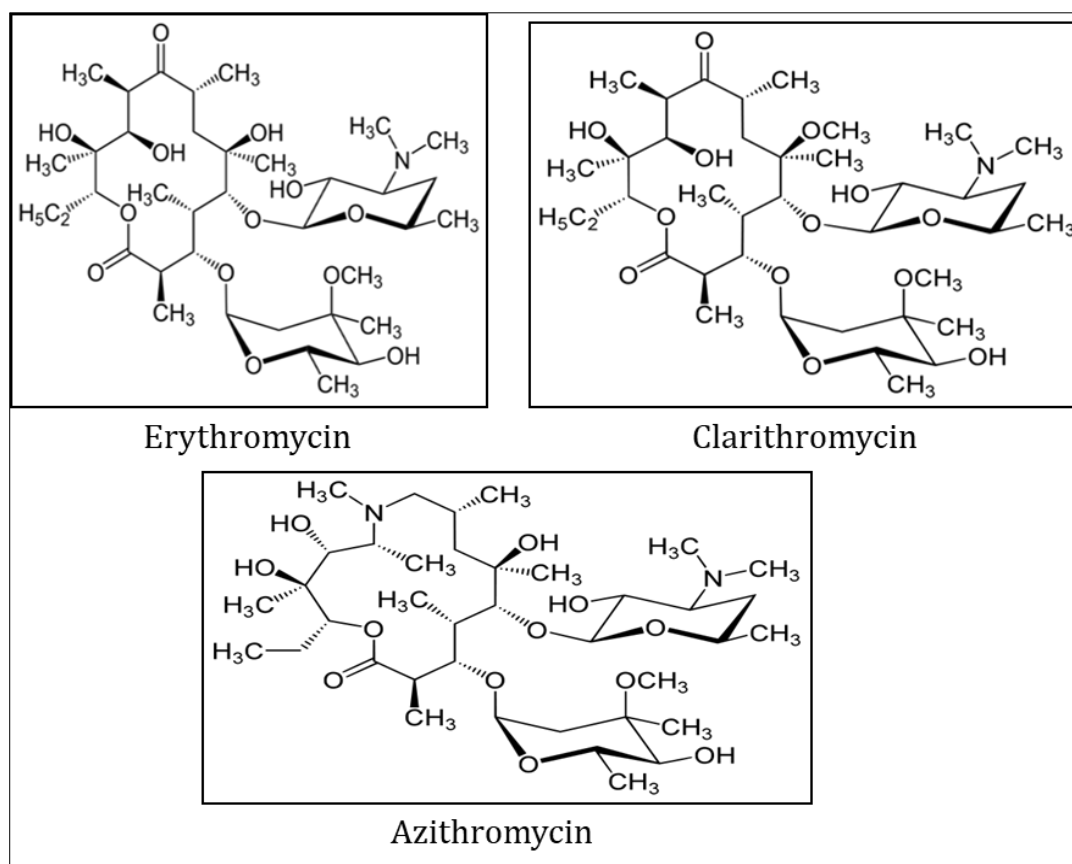
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Erythromycin in rare cases can lead to liver problems (cholestatic hepatitis) and also inhibits cytochrome P450 and thus enhances the effect of oral anticoagulants and digoxin [6]. It is not possible to define exactly whether there is cross-sensitivity between macrolides, it seems to be possible, so in case of allergy to one macrolide, the tolerability of one of the other macrolides should be examined [7]. Since hypersensitivity to macrolides is very rare, this paper aimed to confirm the findings so far and to see if there are any significant differences between the urban and rural population when it comes to allergies to macrolides.

### 1.1. Macrolide structure

Macrolide activity is due to the presence of a macrolide ring, a large macrocyclic lactone ring to which one or more deoxy sugars are usually attached, most commonly cladinose and desosamine. Lactone rings are usually 14-, 15-, or 16-membered. Macrolides belong to the class of natural products, polyketides [8]. Azithromycin is produced from erythromycin, by chemical transformation of the macrolide ring, i.e. by introducing nitrogen into the lactone ring [9].

The only difference between clarithromycin and erythromycin is in one methylated hydroxyl group of the lactone ring. This small chemical modification improves the properties of clarithromycin, so unlike erythromycin, clarithromycin is stable in the acidic medium of the stomach, is more quickly resorbed from the digestive system and is more effective against streptococci and staphylococci than erythromycin.

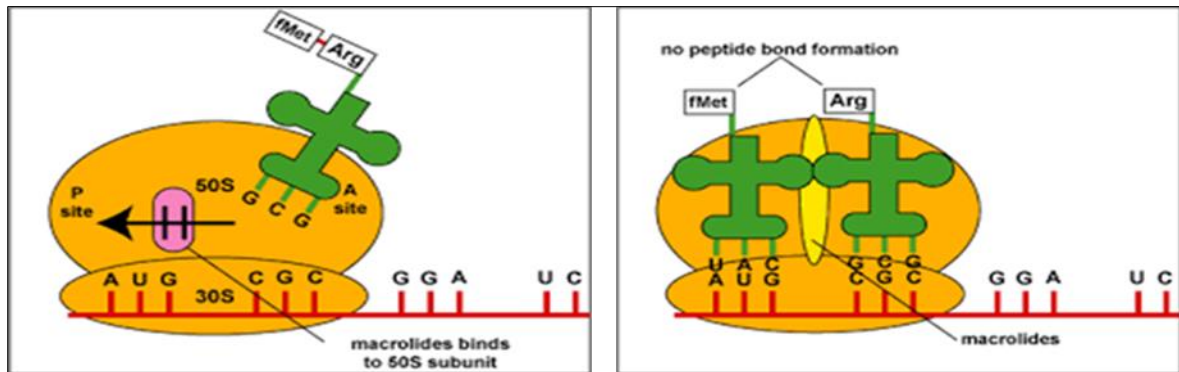


**Figure 1** Chemical structure of macrolides (Nina S. Božinović, 2017)

### 1.2. Mechanism and Spectrum of action

Macrolides have a relatively broad spectrum of action and a high therapeutic index. They act on most aerobic and anaerobic gram-positive bacteria, mycoplasma, chlamydia and rickettsiae, and very weakly on gram-negative bacteria. Erythromycin, clarithromycin and azithromycin belong to this group of antibiotics. They bind to the 50S subunit of the prokaryotic ribosome and prevent aminoacyl translocation [10]. These antibiotics act on microorganisms in the reproductive phase, and depending on the concentration and type of microorganism, they can have a bacteriostatic and bactericidal effect.

Namely, macrolides bind reversibly to the 50S subunit of the bacterial ribosome and thus inhibit the activity of the enzyme peptidyltransferase, which creates peptide bonds between amino acids, which disable the formation of a polypeptide chain or will disable the transition of tRNA from aminoacyl to peptidyl tRNA site.



**Figure 2** Mechanism of action of macrolides (S. Makovec et al., 2014: Croatian Journal of Food Technology, Biotechnology and Nutrition 9)

### 1.3. Place in Therapy

The antimicrobial spectrum of macrolides is somewhat broader than penicillin, and is therefore often used as a substitute in patients allergic to penicillin. Due to the relatively wide spectrum of action, the possibility of oral administration and harmlessness, macrolide antibiotics occupy an important place in the treatment of infectious diseases.

Erythromycin is very effective in combating the most common bacterial pathogens of the respiratory system. Due to the one-day dosage, the high tissue and cellular concentrations it achieves, the possibilities of use in pregnancy and in children, azithromycin is one of the best-selling drugs in the world. It is prescribed to adults for acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia caused by *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* and *Streptococcus pneumoniae*, and inflammation of the pharynx and tonsils caused by the first bacterium *Streptococcus*. It is also given for uncomplicated skin and soft tissue infections caused by *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococcus agalactiae*, urethral and cervical infections with *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Haemophilus malaxia*, teksaria, texiaria, protiksaria [8]. It also shows great efficiency in Lyme disease transmitted by ticks.

Clarithromycin is used to treat mostly the same or similar infections as erythromycin and azithromycin. Clarithromycin (along with amoxicillin and omeprazole) is used in the therapy of eradication of *Helicobacter pylori* from the stomach where it causes gastric ulcer.

In addition to chronic respiratory diseases, there is growing evidence of the applicability of macrolide antibiotics as immunomodulatory agents for inflammatory bowel disease, arthritis, and inflammatory skin diseases such as rosacea and psoriasis [11].

## 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**

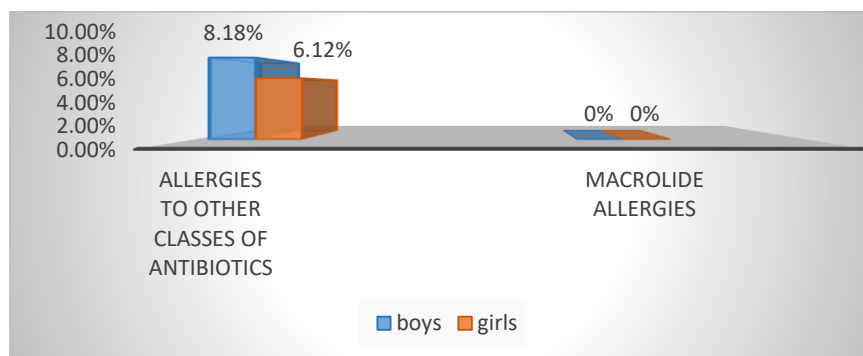
After data collection, the division into gender categories and data collection area was performed, and then for each sex certain age categories and settlements were calculated basic statistical parameters and statistical significance ( $\chi^2$ -test hi-square), between the compared categories of respondents. 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**

The results of the research on the occurrence of allergies to macrolides in the population of 15 years of urban settlement are shown in Table 1 and Figure 3.

**Table 1** Percentage of occurrence of allergic reactions to macrolides in the population of 15 years of urban area

	Allergies on other classes of antibiotics		Macrolide allergies
	Yes	No	
Boys	27 (8.18%)	303 (91.8%)	-
Girls	18 (6.12%)	276 (93.9%)	-
Total	45 (7.2%)	579 (92.8%)	-



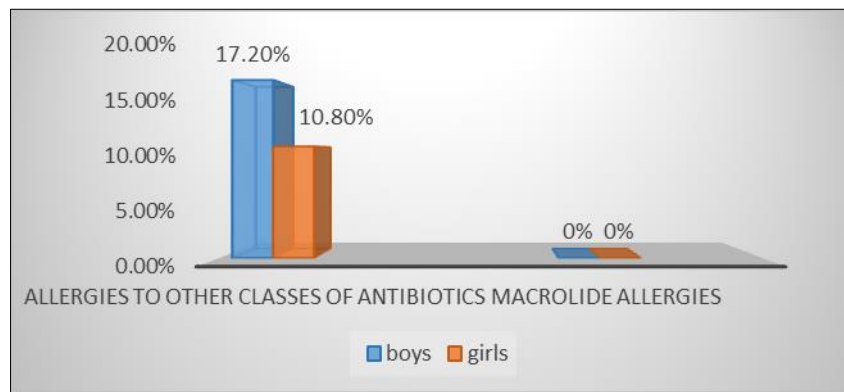
**Figure 3** Differences in the occurrence of allergic reactions to antibiotics between boys and girls aged 15 from the city of Tuzla

The data in Table 1 show that 8.18% of boys and 6.12% of girls are allergic to some type of antibiotic, and allergies to macrolides were not found in any of the observed groups.

The results of the research on the occurrence of allergies to macrolides in the population of 15 years of suburban settlement are shown in Table 2 and Figure 4.

**Table 2** Percentage of occurrence of allergic reactions to macrolides in the population of 15 years of suburban area

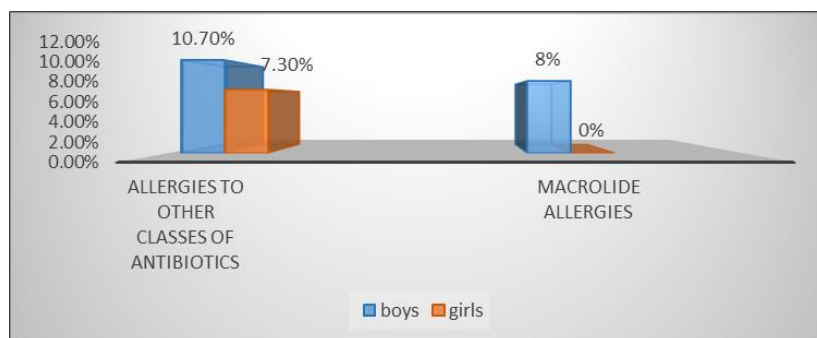
	Allergies on other classes of antibiotics		Macrolide allergies
	Yes	No	
Boys	20 (17.2%)	96 (82.76%)	-
Girls	27 (10.8%)	223 (89.2%)	-
Total	47 (12.8%)	319 (87.2%)	-



**Figure 4** Differences in the occurrence of allergic reactions to antibiotics between boys and girls aged 15 from suburban area of city Tuzla

**Table 3** Percentage of occurrence of allergic reactions to macrolides in the population of 15 years from rural area

	Allergies on other classes of antibiotics		Macrolide allergies
	Yes	No	
Boys	24 (10.7%)	200 (89.3%)	2 (8.3%)
Girls	24 (7.3%)	309 (93.6%)	0.0
Total	48 (8.6%)	509 (91.4%)	2 (0.36%)



**Figure 5** Differences in the occurrence of allergic reactions to macrolides between boys and girls aged 15 from rural area

Table 2 shows that the percentage of allergy to antibiotics is 17.2% in the group of boys and 10.8% in the group of girls. No allergies to macrolides were found between the observed groups.

The results of the research on the occurrence of allergies to macrolides in the population of 15 years of rural areas are shown in Table 3 and Figure 5.

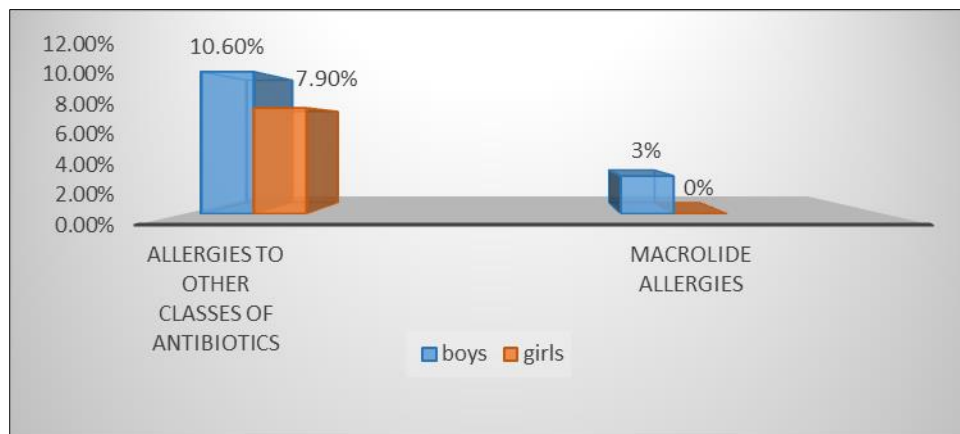
Table 3 shows that in the 15-year-old population of the rural settlement, 10.7% of boys and 7.3% of girls are allergic to the medical type of antibiotic. Macrolide allergies were reported only in the boy group and accounted for 8.3% of all other allergies in boy's group and only 0.36% of this study population is allergic to macrolides.

Table 4 shows data on the occurrence of allergic reactions in the total sample of boys and girls in Tuzla Canton.

Data show that in the total sample, 10.6% of boys and 7.9% of girls are allergic to antibiotics. Of these, only 0.14 % of the population is allergic to macrolides.

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

	Allergies on other classes of antibiotics		Macrolide allergies
	Yes	No	
Boys	71(10.6%)	599 (89.4%)	2 (2.82%)
Girls	69 (7.9%)	805 (92.1%)	0.0
Total	140 (9.1%)	1404 (91.0%)	2 (0.14%)



**Figure 5** Differences in the occurrence of allergic reactions to antibiotics between boys and girls aged 15 from Tuzla canton

**Table 5** Differences in the occurrence of allergic reactions to macrolide between the observed groups of subjects (boys and girls)

Compared categories	N	df	Phi value	Cramer's value	Contingency coefficient	Pearson Chi-Square	Sig. (p)
All Boys-Girls aged 15 years.	140	1	0.119	0.119	0.118	1.972	0.160
City-Village	140	1	-0.167	0.167	0.164	3.899	0.049

Table 5 shows whether there is a statistically significant difference in the occurrence of macrolide allergy between male and female populations, as well as between urban and rural populations.

The data do not show a statistically significant difference between the male and female population, but show a statistically significant difference between the urban and rural population.

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#### **4. Discussion**

The results of the research (Table 1) show that 7.2% of the total population of boys and girls aged 15 in the area of the city of Tuzla is allergic to some kind of antibiotic. Allergies to macrolides were not found in any of the observed groups.

In the suburbs, allergies to antibiotics are more common -12.8% of the population is allergic to antibiotics, but no cases of allergy to macrolides have been reported here either.

Cases of macrolide allergy have been reported in the rural population and account for 8.3% of all antibiotic allergies present in the boy's group.

The data in Table 4 show that in the total sample of respondents, boys and girls aged 15 in Tuzla Canton, as many as 9.1% of them are allergic to some type of antibiotic. About 0.14% of this population is allergic to macrolides. Allergies are observed in a higher percentage in the group of boys, regardless of whether they are from urban or rural areas. Macrolide allergies were also reported only in the group of boys.

Statistically significant differences in the occurrence of macrolide allergies were not observed between the group of boys and girls, but exist between the respondents of urban and rural settlements.

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#### **5. Conclusion**

Antibiotic allergies are in most cases present in suburban and rural settlements compared to urban. Research has confirmed that allergies to macrolide antibiotics are very rare. Interestingly, a higher percentage of allergic reactions to antibiotics are always present in the group of boys. It is also interesting that allergies to macrolide antibiotics were not found in any of the examined categories except in the group of boys from rural areas and make only 0.36% of all allergic reactions in that population. It was found that there are no statistically significant differences in the occurrence of allergic reactions to macrolides between boys and girls but statistically significant differences exist between the population in urban and rural settlements.

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 suburban settlements, whether they are environmental factors, lifestyle or more frequent prescribing of certain antibiotics in some 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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