



# Antimicrobial susceptibility of bacteria causing uncomplicated cystitis in Slovenia

Občutljivost za antibiotike pri povzročiteljih nezapletenega cistitisa v Sloveniji

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## Abstract

**Background:** Acute uncomplicated cystitis in women is a common reason for antibiotic treatment in the outpatient clinic of family doctors. Microbiological diagnostics is not indicated, treatment is generally empirical and based on guidelines and recommendations. Therefore, we do not have representative data on the incidence and sensitivity of pathogens from regular laboratory work. Special targeted research is needed.

**Methods:** We present the results of a prospective study conducted in four regional laboratories of the Centre for Medical Microbiology NLZOH between 15 September 2017 and 31 December 2019. We included 110 female patients with suspected acute uncomplicated cystitis who completed a questionnaire and submitted urine samples for microbiological examination.

**Results:** The result of urine examination was positive in 79 patients (71.8%). Among all isolates, the most common bacterium was *Escherichia coli* (74%), followed by *Staphylococcus saprophyticus* (10%), and others. The susceptibility of *E. coli* to trimethoprim with sulfamethoxazole was 85.5%, to nitrofurantoin 98.4%, and to fosfomicin 100%. *S. saprophyticus* isolates were susceptible to the tested antibiotics except for fosfomicin, against which the bacterium is intrinsically resistant. The total susceptibility of all isolates was 85.8% - 88.2% for trimethoprim with sulfamethoxazole, 88.1% - 95.2% for nitrofurantoin, 73.8% - 80.8% for fosfomicin, 72.6% for ampicillin and amoxicillin, 97.7% for cefadroxil and 98.9% for amoxicillin with clavulanate acid. A comparison with the results of monitoring bacterial resistance as part of the regular work of microbiological laboratories shows significant differences for most of the tested antibiotics.

**Conclusion:** The research results show a relatively good susceptibility of the causative agents of acute uncomplicated cystitis to oral antibiotics, the only exception being amoxicillin.

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## Izveček

**Izhodišče:** Akutni nezapleteni cistitis pri ženskah je pogost razlog za zdravljenje z antibiotiki v ambulantni družinskih zdravnikov. Mikrobiološke preiskave niso indicirane, zdravljenje je praviloma izkustveno in temelji na smernicah in priporočilih. Zato reprezentativnih podatkov o pojavnosti in občutljivosti povzročiteljev iz rednega dela laboratorijev nimamo. Potrebne so posebne usmerjene raziskave.

**Metode:** V prispevku obravnavamo rezultate prospektivne raziskave, ki smo jo v štirih regionalnih laboratorijih Centra za medicinsko mikrobiologijo NLZOH izvedli v času od 15. 9. 2017 do 31. 12. 2019. V raziskavo smo vključili 110 bolnic s sumom na akutni nezapleteni cistitis, ki so izpolnile vprašalnik in oddale vzorec seča za urinokulturo.

**Rezultati:** Rezultat preiskave seča je bil pozitiven pri 79 bolnicah (71,8 %). Med vsemi izolati je bila najpogostejša bakterija *Escherichia coli* (74 %), sledila je bakterija *Staphylococcus saprophyticus* (10 %) in druge. Občutljivost *E. coli* za trimetoprim s sulfometoksazolom je bila 85,5 %, za nitrofurantoin 98,4 % in za fosfomicin 100 %. Izolati *S. saprophyticus* so bili dobro občutljivi za vse testirane antibiotike razen za fosfomicin, proti kateremu je bakterija naravno odporna. Skupna občutljivost vseh izolatov je bila za trimetoprim s sulfometoksazolom 85,8–88,2 %, za nitrofurantoin 88,1–95,2 %, za fosfomicin 73,8–80,8 %, za ampicilin in amoksicilin 72,6 %, za cefadroksil 97,7 % in za amoksicilin s klavulansko kislino 98,9 %. Primerjava z rezultati spremljanja odpornosti bakterij v okviru rednega dela mikrobioloških laboratorijev kaže velike razlike pri večini testiranih antibiotikov.

**Zaključek:** Rezultati raziskave kažejo razmeroma dobro občutljivost povzročiteljev akutnega nezapletenega cistitisa za peroralne antibiotike, izjema je le amoksicilin.

## 1 Introduction

Acute uncomplicated cystitis (AUC) is an infection in women aged 18 to 65 who do not have risk factors for a more severe course or complicated infection, such as anatomical or functional abnormalities of the urinary tract, pregnancy, chronic diseases (e.g. diabetes) or treatments that lower the body's defences, previous urinary tract surgery, urinary catheterisation, etc. (1). It is one of the most common reasons for women to visit their family doctor (1,2).

Treatment of AUC is usually empirical. In Slovenia, nitrofurantoin and fosfomicin are the recommended drugs, the same as provided in European guidelines (3,4). If the proportion of resistant *Escherichia coli* isolates is less than 20%, trimethoprim/sulfamethoxazole (TMP/SMX) can be used; we can also use amoxicillin with clavulanic acid or cephalosporins, regardless of the proportion of resistant *E. coli* isolates (1,3-5). Amoxicillin without clavulanic acid is discouraged by European guidelines because of the high proportion of resistant *E. coli*, and the use of fluoroquinolones is very limited because of the potential for serious side effects (3,6).

Microbiological diagnosis is not indicated in AUC, and infection treatment is empirical and based on national recommendations. Exceptions are patients with atypical symptoms or if the initial antibiotic was ineffective (3). Therefore, the routine work of microbiology laboratories does not provide us with representative data on the pathogens, their antimicrobial susceptibility, and the

appropriateness of the recommendations for empirical treatment. For this reason, studies involving patients with AUC have been carried out in several countries (5,7-9). The results showed large differences between countries, especially in the proportions of antibiotic-resistant isolates. Thus, an AUC survey is needed in every country. To our knowledge, one has not yet been carried out in Slovenia. The Slovenian recommendations for TMP/SMX are based on data from routine work of microbiology laboratories, which includes diagnostics of all clinical samples; the data is available on the website of the Slovenian National Antimicrobial Susceptibility Testing Committee (SKUOPZ) (10).

In September 2017, the Centre for Medical Microbiology of the National Laboratory of Health, Environment and Food (NLZOH), with the participation of physicians from general and family outpatient clinics in the regions of Nova Gorica and Gorenjska, started a targeted prospective study involving patients with a clinical picture that met the definition of AUC. The design and implementation of the study followed the example of studies carried out in European countries (7-9). In April 2018, the study was extended to the region of Novo mesto, and two months later, to the region of Celje (11). This paper presents the results of the tests carried out until the end of the study, i.e., from 15 September 2017 to 31 December 2019. The study results were compared with the results of resistance monitoring in samples from routine work of microbiological laboratories.

## 2 Material and methods

This paper presents the results of the microbiological examination of urine samples from patients in four departments of the Centre for Medical Microbiology of the NLZOH in Nova Gorica, Kranj, Novo mesto, and Celje in the period from 15 September 2017 to 31 December 2019.

Patients aged 18 to 65 years with AUC symptoms without factors for complicated infection were invited to participate in the study at the time of examination in an outpatient clinic of family doctors. A total of 8 healthcare institutions participated: 6 health centres (ZD Nova Gorica, ZD Radovljica, ZD Tržič, ZD Kranj, ZD Trebnje, ZD Celje), the Vitalija General Medicine Outpatient Clinic and the RR Private Health Centre. There were 115 patients willing to participate. Five patients did not meet the eligibility criteria; thus, 110 were included in the study. At the time of examination, patients signed a consent form and completed a questionnaire with demographic data, data on signs and symptoms of infection, and exclusion criteria for AUC. The physician excluded complicated infections and upper urinary tract infections and completed the questionnaire with the antibiotic prescribed at the time of examination (12).

Before the start of treatment, patients submitted a clean-catch midstream urine sample for testing. The samples were examined using the semi-quantitative urine culture method with standard procedures, and the results were discussed according to the European guidelines (13,14).

In the study, we treated 110 patients who met the eligibility criteria for inclusion. The patients were aged 18–65 years, with a mean age of 42.6 years. We treated 76 patients (69.1%) in the laboratory in Kranj, 19 patients (17.3%) in Nova Gorica, 11 patients (10%) in Celje, and 4 patients (3.6%) in Novo mesto. Only isolates from the 79 patients with positive urine culture results were included for further analysis of the pathogens and their antimicrobial susceptibility.

Antimicrobial susceptibility was determined by the disk diffusion method, and the results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (15–17). According to the EUCAST guidelines, the result for nitrofurantoin is only valid for uncomplicated urinary tract infections; for Enterobacteriaceae, the interpretation is only valid for *E. coli*, for enterococci only for *Enterococcus faecalis*, for staphylococci only for *Staphylococcus saprophyticus*, and for beta-haemolytic streptococci only for *Streptococcus agalactiae* (15–17). Under the EUCAST guidelines, interpretation for oral fosfomycin (fosfomycin trometamol) is only valid for uncomplicated urinary tract infections, and there is no interpretation for other infections. Up to and including 2020, the interpretation was given for all Enterobacteriaceae, and from 2021

onwards, due to stricter criteria only for the *E. coli* species (15–18). There is no interpretation for fosfomycin for other bacteria (*E. faecalis*, *S. agalactiae*, etc.), and *S. saprophyticus* is intrinsically resistant to fosfomycin (15–19).

In some cases, the clinical efficacy of the antibiotic is not sufficiently known, so interpretation of the result according to EUCAST guidelines is not possible; these combinations of bacteria/ antibiotic were not tested: for *E. faecalis*, the efficacy of TMP/SMX is not known; for *Klebsiella* spp. and *Citrobacter* spp., there is insufficient data to support the efficacy of nitrofurantoin, for *Enterobacteriaceae* other than *E. coli*, there is insufficient data to support the efficacy of oral fosfomycin.

In order to establish the efficiency of particular antibiotics (expressed as the ratio of the number of isolates susceptible to a particular antibiotic to the number of all isolates), we looked at the prevalence of each bacterial species and grouping among all isolates and the proportion of each species or grouping that is susceptible to a particular antibiotic. The contribution to the susceptibility of a bacterial species is the product of the prevalence and the proportion of antimicrobial susceptibility of isolates of that species. For example, the proportion of *E. coli* among all isolates in the study was 0.738; the susceptibility to nitrofurantoin was 100%, which means that *E. coli* contributes the product of 0.738 and 100%, i.e., 73.8%, to the susceptibility to nitrofurantoin. For bacteria/antibiotic combinations for which the clinical efficacy is not sufficiently known and for which there is no interpretation, but according to the EUCAST documents, the effect is possible, and the proportion of susceptibility is indicated in a range of susceptibility from 0% to 100% (20–22).

A positive opinion for conducting the study was obtained from the National Medical Ethics Committee of the Republic of Slovenia (No 0120-455/2016-2, KME 40/09/16).

**Table 1:** Number and prevalence of isolates from urine samples in women with acute uncomplicated cystitis.

Bacteria	number	prevalence
<i>Escherichia coli</i>	62	0.74
<i>Staphylococcus saprophyticus</i>	8	0.10
<i>Proteus mirabilis</i>	4	0.05
<i>Streptococcus agalactiae</i>	3	0.04
<i>Klebsiella</i> spp.	3	0.04
<i>Citrobacter koseri</i>	2	0.02
<i>Enterococcus faecalis</i>	2	0.02
Total	84	

**Table 2:** Number and proportion of isolates from urine samples in women with acute uncomplicated cystitis according to age groups.

Age group	No. of patients	No. and proportion (%) of patients with positive urinalysis	No. of isolates total	No. and proportion of isolates by species				
				<i>E. coli</i> N (%) <sup>*</sup>	<i>S. saprophyticus</i> N (%) <sup>*</sup>	<i>S. agalactiae</i> N (%) <sup>*</sup>	<i>P. mirabilis</i> N (%) <sup>*</sup>	Others N (%) <sup>*</sup>
18-30 yrs	25	21 (84.0)	22	12 (57.1)	6 (28.6)	0	2 (9.5)	2 (9.5)
31-40 yrs	27	19 (70.4)	20	16 (84.2)	1 (5.3)	1 (5.3)	0	2 (10.5)
41-50 yrs	22	12 (54.5)	13	12 (100.0)	0	0	1 (8.3)	0
51-65 yrs	36	27 (75.0)	29	22 (81.5)	1 (3.7)	2 (7.4)	1 (3.7)	3 (11.1)
Total	110	79 (71.8)	84	62 (78.5)	8 (10.1)	3 (3.8)	4 (5.1)	7 (8.9)

Legend: yrs – years. \* The proportion of isolates relative to the number of patients with a positive urine culture in percentage. The number of isolates is small, so proportions should be treated with caution.

### 3 Results

The result of microbiological urinalysis was positive in 79 patients (71.8%) and negative in 24 patients (21.8%); in 7 patients (6.4%) three or more different types of bacteria

were isolated, which was defined as probable contamination of the sample at the time of collection; the investigation was completed without an antibiogram. Among the positive samples, 74 cases (93.7%) had one species of bacteria, and five cases (6.3%) had two species each.

**Table 3:** Antimicrobial susceptibility and resistance of *E. coli* isolates from urine samples in women with acute uncomplicated cystitis.

Antibiotic	No. of tested <i>E. coli</i> isolates	Proportion of <i>E. coli</i> isolates susceptible to the antibiotic %	Proportion of <i>E. coli</i> isolates resistant to the antibiotic
trimethoprim/sulfamethoxazole	62	85.5	14.5
nitrofurantoin	62	98.4	1.6
fosfomicin trometamol	58	100	0
norfloxacin	53	98.1	1.9
ciprofloxacin	62	98.4	1.6
ampicillin (and amoxicillin)*	62	72.6	27.4
amoxicillin with clavulanic acid – interpretation for uncomplicated cystitis	62	98.4	1.6
amoxicillin with clavulanic acid – interpretation for systemic infections	62	95.2	4.8
cefadroxil	58	100	0
cefuroxime axetil	62	100	0
cefixime	58	100	0

Legend: \* According to the EUCAST guidelines, the result for ampicillin is also valid for amoxicillin.

The number and prevalence of identified AUC pathogens are shown in Table 1, while the number and proportion of isolates by age group are presented in Table 2. *E. coli* was the prevalent bacterium among the isolates (62 isolates, 74%), followed by *S. saprophyticus* (8 isolates, 10%) and *P. mirabilis* (4 isolates, 5%), with the proportion of the remaining bacteria being less than 5%. In all age groups, *E. coli* was predominant. In the age group of 18 to 30 years, the proportion of *E. coli* was the smallest, 57.1%, and the proportion of *S. saprophyticus* was the largest, 28.6%. In the other age groups, the proportion of *E. coli* exceeded 80%, and the proportion of *S. saprophyticus* was 5% or less.

The mean age of *E. coli* patients was 44 years, and of *S. saprophyticus* patients, 30 years.

Antimicrobial susceptibility is shown in Tables 3 and 4. The susceptibility of *E. coli* strains to TMP/SMX was 85.5%, to nitrofurantoin 98.4%, and to fosfomicin trometamol

(oral fosfomicin) 100%. *E. coli* strains and other *Enterobacteriaceae* with extended-spectrum beta-lactamases (ESBLs) were not detected.

For *E. coli*, 42 isolates (67.7%) were susceptible to all tested antibiotics. Resistance to one antibiotic was found in 12 isolates (19.4%). Resistance to two or more antibiotics was found in 8 isolates (12.9%): 6 isolates (9.7%) were resistant to both ampicillin and TMP/SMX, one isolate (1.6%) was resistant to both ampicillin and amoxicillin with clavulanic acid (interpretation for uncomplicated cystitis), and one isolate (1.6%) was resistant to TMP/SMX, ciprofloxacin and norfloxacin.

All *S. saprophyticus* isolates (8 isolates) were susceptible to all tested antibiotics: TMP/SMX, nitrofurantoin, ciprofloxacin, cefoxitin, ampicillin, and tetracycline. The result for ampicillin also holds for amoxicillin and amoxicillin with clavulanic acid (17). All three isolates of *Streptococcus*

**Table 4:** Antimicrobial susceptibility of isolates from urine samples in women with acute uncomplicated cystitis.

Bacteria / antibiotic	No of isolates	Prevalence of the bacterial species or group	Proportion of susceptible strains among all isolates in percent								
			nitrofurantoin	trimethoprim/sulfamethoxazole	ampicillin and amoxicillin	amoxicillin with clavulanic acid	fosfomicin trometamol	cefadroxil	cefuroxime axetil	cefixime	ciprofloxacin
<i>Escherichia coli</i>	62	0.738	72.6	63.1	53.6	72.6 <sup>(1)</sup>	73.8	73.8	73.8	73.8	72.6
<i>Staphylococcus saprophyticus</i>	8	0.095	9.5	9.5	9.5	9.5 <sup>(5)</sup>	0 <sup>(2)</sup>	9.5	9.5	9.5	9.5
<i>Streptococcus agalactiae</i>	3	0.036	3.6	3.6	3.6 <sup>(4)</sup>	3.6 <sup>(4)</sup>	0 <sup>(6)</sup>	3.6	3.6	3.6	0 <sup>(6)</sup>
<i>Proteus mirabilis</i>	4	0.048	0 <sup>(2)</sup>	3.6	3.6	4.8	0–4.6 <sup>(3)</sup>	4.8	4.8	4.8	2.4
<i>Klebsiella</i> spp.	3	0.036	0–3.6 <sup>(3)</sup>	3.6	0	3.6	0 <sup>(6)</sup>	3.6	3.6	3.6	3.6
<i>Citrobacter koseri</i>	2	0.024	0–2.4 <sup>(3)</sup>	2.4	0	2.4	0–2.4 <sup>(3)</sup>	2.4	0 <sup>(6)</sup>	2.4	2.4
<i>Enterococcus faecalis</i>	2	0.024	2.4	0–2.4 <sup>(3)</sup>	2.4	2.4 <sup>(5)</sup>	0 <sup>(6)</sup>	0 <sup>(6)</sup>	0 <sup>(6)</sup>	0 <sup>(6)</sup>	2.4
Total	84	1	88.1–95.2	85.8–88.2	72.6	98.9	73.8–80.8	97.7	95.3	97.7	92.9

Legend:

<sup>(1)</sup> Interpretation for uncomplicated cystitis.

<sup>(2)</sup> The isolate is intrinsically resistant to the antibiotic.

<sup>(3)</sup> In the EUCAST guidelines, there are no criteria for the interpretation of the antibiogram result, the efficacy of the antibiotic for the bacterium is not (sufficiently) known, the outcome of the treatment cannot be predicted, but according to the EUCAST documents, the effect is possible, the sensitivity is indicated in the interval (20–22).

<sup>(4)</sup> The results for ampicillin, amoxicillin and amoxicillin with clavulanic acid are inferred from the result for benzylpenicillin.

<sup>(5)</sup> The result for ampicillin is also valid for amoxicillin with clavulanic acid.

<sup>(6)</sup> In the EUCAST guidelines, there are no criteria for the interpretation of the antibiogram result; the efficacy of the antibiotic for the bacterium is not sufficiently known and is not recommended for treatment (22).

*agalactiae* were susceptible to TMP/SMX, nitrofurantoin, ampicillin, amoxicillin, tetracycline, and vancomycin. There is no interpretation for fosfomycin and ciprofloxacin in *S. agalactiae*; the antibiotics are ineffective in this species (15-17). *E. faecalis* isolates were susceptible to nitrofurantoin, ciprofloxacin, ampicillin, amoxicillin, and vancomycin.

Among the *Klebsiella* spp. isolates, *Citrobacter koseri* and *P. mirabilis* (9 isolates in total), the proportion of susceptible strains was 88.9% for TMP/SMX, 85.7% for ciprofloxacin, 77.8% for norfloxacin, and 33.3% for ampicillin and amoxicillin; all tested strains were susceptible to the other antibiotics, i.e. amoxicillin with clavulanic acid and oral cephalosporins (cefadroxil, cefuroxime axetil, and cefixime). *P. mirabilis* species are intrinsically (naturally) resistant to nitrofurantoin, whereas there is no interpretation for *Klebsiella* spp. and *Citrobacter* spp. (15-18).

Table 4 shows the overall susceptibility of all isolates to a specific antibiotic, taking into account the prevalence of each bacterial species or grouping among all isolates and the proportion of susceptibility of each species or grouping to a specific antibiotic. For bacteria naturally (intrinsically) resistant to a particular antibiotic (*P. mirabilis* to nitrofurantoin and *S. saprophyticus* to fosfomycin), zero percent are indicated for the proportion of susceptible strains.

The overall susceptibility of all isolates was 85.8%–88.2% for TMP/SMX, 88.1%–95.2% for nitrofurantoin,

73.8%–80.8% for fosfomycin, 72.6% for ampicillin and amoxicillin, 97.7% for cefadroxil, and 98.9% for amoxicillin with clavulanic acid.

Table 5 compares the *E. coli* susceptibility results of the present study with the results of the 2017 SKUOPZ susceptibility monitoring and the results of the routine work of NLZOH in 2016 (urine testing of patients of both genders aged 15 to 65) (10,23). The SKUOPZ monitoring includes bacterial susceptibility results from the routine work of microbiology laboratories. It includes all clinical samples, and it is impossible to separate results from individual samples (e.g., urine) (10).

## 4 Discussion

An average of one in two women will experience AUC at least once in their lifetime, with infections often recurring (24-26). AUC is thus a common reason for antibiotic treatment in primary healthcare (26). The infection is usually treated empirically with as narrow-spectrum antibiotic as possible, which acts on the most common pathogens of AUC. The drugs of choice are nitrofurantoin and fosfomycin trometamol. An alternative treatment is TMP/SMX, provided that the proportion of resistant *E. coli* strains is less than 20% (1,3-5). If the above antibiotics cannot be prescribed to the patient or are poorly tolerated by the patient,

**Table 5:** Comparison of the proportions of antibiotic-susceptible *E. coli* in three studies.

Study	SKUOPZ 2017	urine samples from both genders (2016)	acute uncomplicated cystitis (2017-2019)
No. of <i>E. coli</i> isolates	17,990-24,272	565	62
antibiotic	proportion of susceptible strains in percent		
nitrofurantoin	99	99.6	98.4
fosfomycin trometamol	NDA	NDA	100
trimethoprim/sulfamethoxazole	70.2	62.7	85.5
ciprofloxacin	78.1	86.2	98.4
amoxicillin with clavulanic acid – interpretation for uncomplicated cystitis	89.4	92.4	98.4
amoxicillin with clavulanic acid – interpretation for systemic infections	79.9	82.3	95.2
proportion of ESBL strains in per cent	8.3	3.5	0

Three studies: 1) susceptibility monitoring of isolates from all clinical samples in 2017 in the context of the SKUOPZ (10), 2) data from urine isolates of patients of both genders aged 15–65 from the routine work of two microbiology laboratories of the NLZOH in 2016 (23), and 3) the results of the study on uncomplicated cystitis (women aged 18–65; 15 September 2017 to 31 December 2019).

Legend: NDA – no data available ESBL – extended-spectrum beta-lactamases.

AUC can be treated with beta-lactam antibiotics: amoxicillin with clavulanic acid or cephalosporins. These are broad-spectrum antibiotics that have an adverse ecological impact (3). Amoxicillin without clavulanic acid is discouraged by European guidelines due to the high proportion of resistant *E. coli* (3). The European Medicines Agency has severely restricted the use of fluoroquinolones in recent years due to the severe side effects observed, and they can only be used to treat AUC in exceptional cases where treatment with another effective antibiotic is not possible (6).

As microbiological testing is not indicated in patients with AUC, with a few exceptions, data from routine work of microbiology laboratories is not helpful in planning empirical treatment and monitoring the appropriateness of the recommendations for the treatment of AUC. Periodic targeted examinations of AUC patients are needed. To our knowledge, the present study conducted at the NLZOH from 15 September 2017 to 31 December 2019 is the first AUC study in Slovenia. Previously, results of urine samples for the diagnosis of urinary tract infections were collected periodically from routine laboratory work. The results from routine work of laboratories mainly include samples from patients with complicated upper and lower urinary tract infection, from patients with recurrent infection or from patients in whom initial treatment of urinary tract infection has not been effective (23,27-29). Urine samples from patients with AUC are very rare in the routine work of microbiology laboratories and cannot be distinguished from other samples.

In the study, we found 84 bacterial isolates in 79 (71.8%) patients with a positive urine culture. *E. coli* was the most frequently detected bacterium (62 isolates; prevalence among all isolates 0.74), followed by *S. saprophyticus* (8 isolates; prevalence 0.10). Other bacteria were found in smaller numbers. The results are similar to those of studies carried out in other countries (7-9). In the ARESC study, involving 9 European countries and Brazil, the *E. coli* prevalence in 2009 was 68.1% in Austria, 72.6% in Italy, 78.8% in Hungary, and ranged from 72.6% to 83.8% in the other participating countries; the mean range was 76.7%. The proportion of *S. saprophyticus* was 2.2% in Austria, 0% in Italy and Hungary, and ranged from 0% to 5.6% in other countries, with an average of 3.6% (9). The differences between the countries are relatively large and are probably mainly due to the differences in the patients' age.

Microbial susceptibility was relatively good: for *E. coli*, it was 98.4% for nitrofurantoin, 85.5% for TMP/SMX, 100% for oral fosfomycin, and the tested oral cephalosporins (cefadroxil, cefixime and cefuroxime-acetyl), 98.4% for amoxicillin with clavulanic acid as interpreted for uncomplicated urinary tract infections and ciprofloxacin. According to the

EUCAST guidelines, cefadroxil, cefixime and oral cefuroxime are only suitable for treating uncomplicated urinary tract infections (15-18). The results of a study conducted in Austria in 2007 and 2008 were very similar: the resistance of *E. coli* strains to nitrofurantoin was 0.7%, to fosfomycin 0.7%, to TMP/SMX 14.4%, and to ciprofloxacin 4.1% (8). However, compared with the large international ARESC study, the proportion of susceptibility in Slovenia was higher. The ARESC study included 2,315 *E. coli* strains, with a 70.5% susceptibility to TMP/SMX, 95.2% susceptibility to nitrofurantoin, 98.1% susceptibility to fosfomycin, 91.8% susceptibility to ciprofloxacin, 45.1% susceptibility to ampicillin, and 82.1% susceptibility to amoxicillin with clavulanic acid (9).

AUC is an infection occurring in the home environment in otherwise healthy women, and the susceptibility of pathogens is expected to be higher than in patients seen in the routine work of microbiology laboratories. This was confirmed by comparing the *E. coli* susceptibility results of the present study with the results of susceptibility monitoring of isolates from all clinical samples in 2017 in the context of the SKUOPZ and the results of the survey of patients of both genders aged 15-65 from the routine work of the NLZOH in 2016 (10,23). Relatively large differences in susceptibility were found for TMP/SMX, ciprofloxacin, amoxicillin with clavulanic acid, and the proportion of *E. coli* strains with ESBLs. There was no data from routine laboratory work for fosfomycin trometamol; the susceptibility of *E. coli* in the present AUC study was 100%.

*S. saprophyticus* isolates were susceptible to all antibiotics included in the study except fosfomycin trometamol, to which this bacterium is intrinsically resistant (18). The number of isolates was small (8), so we are cautious in our interpretation. As *S. saprophyticus* is mainly responsible for causing AUC and very rarely for other urinary tract infections, results from the routine work of microbiology laboratories are also suitable for susceptibility testing. In a study in which 174 *S. saprophyticus* isolates were tested from urinary tract samples in three microbiology laboratories of the NLZOH from 1 January 2016 to 31 December 2018, susceptibility was found to be from 98% to 100% for TMP/SMX, from 96% to 100% for nitrofurantoin, and from 93% to 96% for ampicillin; the results for ampicillin are also valid for amoxicillin (29).

In order to determine the suitability of each antibiotic for the empirical treatment of AUC, the overall susceptibility of all isolates to oral antibiotics was determined. The overall susceptibility of all isolates was 85.8%-88.2% for TMP/SMX, 88.1%-95.2% for nitrofurantoin, 73.8%-80.8% for fosfomycin trometamol, 72.6% for ampicillin and amoxicillin, 98.9% for amoxicillin with clavulanic acid, 97.7% for

cefadroxil and cefixime, 95.3% for cefuroxime axetil, and 92.9% for ciprofloxacin. Due to their narrow spectrum of action and lower impact on microbial ecology than other antibiotics, nitrofurantoin, fosfomycin trometamol, and TMP/SMX have a significant advantage over cefadroxil, amoxicillin with clavulanic acid, cefuroxime axetil, and cefixime.

Fosfomycin is a broad-spectrum intravenous antibiotic that has historically been used in combination with other antibiotics for treating pneumonia, other lower respiratory tract infections, upper respiratory tract infections, osteomyelitis, and numerous other infections. The fosfomycin derivative, fosfomycin trometamol, is suitable for the oral treatment of AUC caused by *E. coli*. The interpretation of results for fosfomycin trometamol was available in the EUCAST guidelines for all *Enterobacteriaceae* up to and including 2020. However, it was discontinued in 2021 due to stricter requirements for evidence of efficacy. Oral fosfomycin appears to be insufficiently effective for other bacteria, or there is insufficient evidence of clinical efficacy (22). Susceptibility to fosfomycin trometamol was relatively good in this study. The exception is the age group of 18 to 30 years, in which the proportion of *S. saprophyticus* was relatively high (28.6%). Therefore, fosfomycin trometamol is less suitable for treating ANC in this age group. Ampicillin and amoxicillin for the empirical treatment of urinary tract infections are discouraged by the EUCAST due to the high proportion of resistant *E. coli*. Fluoroquinolones (ciprofloxacin and others) are highly effective, but the European Medicines Agency has severely restricted their use due to severe and potentially permanent side effects; in AUC, treatment with fluoroquinolones is limited to cases where no other effective antibiotic is available (6). Treatment with fluoroquinolones also significantly impacts the human microbiota and leads to the selection of resistant bacteria. Scientists have shown that ciprofloxacin treatment reduces the absolute number of *Enterobacteriaceae* in the gut microbiota and increases the proportion of ciprofloxacin-resistant *Enterobacteriaceae*. Colonisation with ciprofloxacin-resistant *Enterobacteriaceae* was also found in people who lived in the same household as ciprofloxacin-treated patients. No increase in the frequency of ciprofloxacin-resistant or nitrofurantoin-resistant strains was detected in nitrofurantoin-treated patients (30).

A limitation of the present study is the small number of patients treated and, consequently, the long duration of the research and the low number of isolates of each species, except *E. coli* isolates. Family doctors in Slovenia have a heavy workload and find it challenging to take on additional responsibilities, which was a key barrier to participation

in the study. Another reason family doctors gave was that there were not as many AUC patients in outpatient clinics as expected.

The study was conducted in four regions, with the highest proportion of patients seen in the Gorenjska region (69.1%). Due to the small number of isolates and so as to monitor trends and establish potential differences between regions, it would be reasonable to repeat the study and include more or maybe even all regions in the country.

## 5 Conclusion

The results of our study have shown that *E. coli* was the most frequently detected bacterium in patients with acute uncomplicated cystitis (74%), followed by *S. saprophyticus* (10%), and the proportion of other bacteria was 5% or less. The susceptibility of *E. coli* to trimethoprim-sulfamethoxazole was 85.5%, to nitrofurantoin 98.4%, and to fosfomycin 100%. *S. saprophyticus* isolates were susceptible to all tested antibiotics except fosfomycin, to which the bacterium is naturally resistant. The overall susceptibility of all isolates was 85.8%–88.2% for trimethoprim-sulfamethoxazole, 88.1%–95.2% for nitrofurantoin, 73.8%–80.8% for oral fosfomycin, 72.6% for ampicillin and amoxicillin, and 98.9% for amoxicillin with clavulanic acid. We believe that the results provide a sound basis for revising the national recommendations for the treatment of acute uncomplicated cystitis and will make an important contribution to the rational use of antibiotics in Slovenia.

## Conflict of interest

None declared.

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