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ANTIBIOTSKA REZISTENCIJA UZROČNIKA INFEKCIJA URINARNOG TRAKTA KOD PACIJENATA INSTITUTA ZA JAVNO ZDRAVLJE KRAGUJEVAC

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SAŽETAK

Uvod/Cilj: Urinarne infekcije su među najčešćim u primarnoj zdravstvenoj zaštiti. Cilj ovog rada je bila mikrobiološka analiza urina ambulantnih pacijenata u Institutu za javno zdravlje u Kragujevcu u periodu od šest meseci (01.11.2020. - 30.04.2021.).
Metod: Retrospektivno, na osnovu prikupljenih rezultata, vršena je identifikacija uzročnika urinarnih infekcija i određivanje njihove osetljivosti na antibiotike metodom antibiograma.
Rezultati: Šestomesečna analiza uzoraka urina ambulantnih pacijenata obuhvatila je 4809 uzoraka urina. Od svih testiranih uzoraka pozitivno na patogene mikroorganizme je bilo 1218 (25,3%). Najzastupljeniji patogeni urinarnog trakta u ispitivanom periodu bili su: *Escherichia coli* 842 (69,1%), *Klebsiella spp*. 252 (20,7%), *Pseudomonas aeruginosa* 71 (5,8%) i *Enterococcus grupa* 53 (4,4%). Bakterija *E. coli* je bila češća kod žena (82,7%), a *Pseudomonas aeruginosa* kod muškaraca (76,1%). *Klebsiella spp*. i *Enterococcus spp*. su se skoro podjednako javljale kod oba pola. Lekovi prvog izbora u terapiji urinarnih infekcija bi bili sledeći: za *E. coli* amikacin (aminoglikozid) i fosfomicin, a za *Klebsiella spp*. meropenem (karbapenem) i takođe amikacin. Što se tiče *P. aeruginosa*, najefikasnijim su se pokazali takođe meropenem, kao i penicilinski antibiotik piperacilin-tazobaktam.
Zaključak: S obzirom na to da uropatogeni poseduju mehanizme za razvoj rezistencije, potrebno je u terapiji koristiti antibiotike u zavisnosti od rezultata antibiograma.

Ključne reči: uropatogeni, antibiotska rezistencija, antibiogram

Uvod

Infekcija urinarnog trakta je jedna od najčešćih infekcija u primarnoj medicinskoj praksi. Svake godine, širom sveta, se dijagnostikuje oko 150 miliona ljudi sa infekcijom urinarnog trakta (bilo da se radi o komplikovanoj ili nekomplikovanoj infekciji). Nekomplikovana urinarna infekcija je češća kod seksualno aktivnih mlađih žena sa anatomsko-fiziološki normalnim urinarnim traktom, dok se komplikovana infekcija češće sreće kod osoba koje imaju neku drugu bolest (prolongirana upotreba antibiotika, dijabetes), abnormalnost urinarnog trakta, prisustvo stranog tela (kateter, kalkulus) i drugo (1).

Antimikrobni agensi su sve hemijske supstance (prirodne i veštačke) i fizički agensi (toplota, UV zračenje, radioaktivno zračenje) koji ubijaju mikroorganizme ili inhibiraju njihov rast. Antimikrobna aktivnost predstavlja najmanju količinu agensa potrebnu za inhibiciju rasta test organizma i naziva se minimalna inhibitorna koncentracija (MIK). Parametri za podelu antimikrobnih lekova su molekularna struktura, mehanizam delovanja i spektar antimikrobne aktivnosti. Grubo se mogu podeliti na: sintetičke antimikrobne lekove i antibiotike (4).

Neki oblici rezistencije (otpornosti) na antimikrobne lekove su urođene osobine određenih grupa mikroorganizama (4). Na primer, mikroorganizmi koji proizvode antibiotike su i otporni na sopstveni proizvod. Ćelijski zid gram-negativnih bakterija nepropustljiv je za penicilin G pa je većina

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ANTIBIOTIC RESISTANCE OF CAUSES OF URINARY TRACT INFECTIONS IN PATIENTS AT THE PUBLIC HEALTH INSTITUTE KRAGUJEVAC

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SUMMARY

Introduction/Aim: Urinary tract infections are one of the most common infections in primary healthcare. The aim of this study was the microbiological analysis of urine of infirmary patients at the Institute of Public Health in Kragujevac during the six-month period (1st November 2020 – 30th April 2021).
Methods: Causes of urinary tract infections were identified retrospectively, according to the collected data, and their sensitivity to antibiotics was determined with the help of antibiogram method.
Results: A six-month analysis of urine samples of infirmary patients included 4809 urine samples. Of all analyzed samples, 1218 (25.3%) were positive to pathogens. The commonest urinary tract pathogens in the examined period were the following: *Escherichia coli* 842 (69.1%), *Klebsiella spp*. 252 (20.7%), *Pseudomonas aeruginosa* 71 (5.8%) and *Enterococcus group* 53 (4.4%). *E. coli* was more frequent in women (82.7%), while *Pseudomonas aeruginosa* was more frequent in men (76.1%). *Klebsiella spp*. and *Enterococcus spp*. were almost equally present in men and women. First-choice drugs in the treatment of urinary infections would be the following: for *E. coli* amikacin (aminoglycoside) and fosfomycin, and for *Klebsiella spp*. meropenem (carbapenem) and also amikacin. As far as *P. aeruginosa* is concerned, meropenem was shown to be the most efficient, as well as the penicillin antibiotic piperacillin-tazobactam.
Conclusion: Considering that uropathogens possess mechanisms for the development of resistance, the treatment should include antibiotics depending on the results of antibiogram.

Key words: uropathogens, antibiotic resistance, antibiogram

Introduction

Urinary tract infections are one of the most common infections in the primary healthcare practice. Every year, 150 million people are diagnosed with urinary tract infections worldwide (complicated or uncomplicated infections). Uncomplicated urinary tract infections are more frequent in sexually active younger women, who have a normal urinary tract in terms of anatomy and physiology, while complicated infections are more common in persons with other diseases (prolonged usage of antibiotics, diabetes), the abnormality of urinary tract, the presence of foreign bodies (catheter, calculus) etc (1).

Antimicrobial agents are all chemical substances (natural and artificial) and physical agents (warmth, UV radiation, radioactive radiation) that kill microorganisms or inhibit their growth. Antimicrobial activity presents the smallest quantity of agents necessary for the inhibition of growth of test organisms and it is called the minimal inhibitory concentration (MIC). Parameters for the classification of antimicrobial drugs are the molecular structure, mechanisms of action and wide spectrum of antimicrobial activity. They can be approximately classified into: synthetic antimicrobial drugs and antibiotics (4).

Some forms of resistance to antimicrobial drugs are innate characteristics of certain groups of microorganisms (4). For example, microorganisms that produce antibiotics are resistant to their own

predstavnika prirodno otporna. Ali kada se govori o rezistenciji na antimikrobne lekove misli se na stečenu otpornost mikroorganizama prema antimikrobnim agensima na koje su oni do tada bili osetljivi.

Antibiotska rezistencija može biti kodirana genima na bakterijskom hromozomu ili na plazmidu koji se naziva R (engl. *resistance*) plazmid (4). Hromozomski kodirana rezistencija je rezultat mutacije u genima za ciljne strukture (kao što su ribozomi, RNK polimeraza, giraza) ili komponente membrane koje učestvuju u izbacivanju antibiotika iz ćelije (efluks pumpe). Široko rasprostranjeni oblici rezistencije kodirani su R plazmidima i mogu se razmenjivati horizontalnim transferom gena. Na R plazmidima se nalaze geni čiji produkti modifikuju (acetilacija, fosforilacija, adenilacija) ili razgrađuju lekove, ili geni koji kodiraju enzime koji mogu da spreče usvajanje antibiotika ili da ih aktivno izbacuju (pumpaju) napolje. Na primer, neki R plazmidi kodiraju β-laktamazu, enzim koji razara β-laktamski prsten, indukujući rezistenciju na peniciline i cefalosporine.

Na svaki antibiotik vremenom će se razviti rezistencija. Konzervativna i svrsishodna upotreba antibiotika može produžiti ili čak povratiti efikasnu kliničku upotrebu nekog antibiotika. Dugotrajno rešenje za antibiotsku rezistenciju zahteva konstantno otkrivanje i razvijanje novih lekova. Nakon pronalaska novog antimikrobnog agensa i testiranja efikasnosti i toksičnosti, potrebne su i dugotrajne kliničke probe na ljudima, što znači da je potrebno oko 10-25 godina da bi se antibiotik mogao upotrebljavati (4).

Cilj ovog rada je bila mikrobiološka analiza urina ambulantnih pacijenata u Institutu za javno zdravlje u Kragujevcu u periodu od šest meseci (01.11.2020. godine - 30.04.2021. godine).

Metode

Istraživanje je sprovedeno retrospektivno na osnovu prikupljenih rezultata šestomesečnih (01.11.2020. godine - 30.04.2021. godine) mikrobioloških analiza koje su obuhvatale izolaciju i identifikaciju bakterijskih uzročnika urinarnih infekcija i određivanje njihove osetljivosti na antibiotike metodom antibiograma. Analiza je vršena na Odeljenju za bakteriologiju i parazitologiju, Centra za mikrobiologiju Instituta za javno zdravlje Kragujevac, na osnovu uputa iz ustanove primarnog nivoa zdravstvene zaštite – Doma zdravlja Kragujevac.

Pozitivan rezultat znači da su patogene bakterijske vrste nađene u signifikantnom (značajnom) broju u uzorku urina pacijenta. Signifikantan broj bakterija u urinu je broj bakterija ≥ 100.000 CFU/ml (engl. *colony forming units per milliliter*) u uzorku srednjeg mlaza urina, što se smatra kriterijumom za potvrdu bakterijske infekcije. Manji broj od toga se smatra kontaminacijom. Nakon adekvatnog uzimanja uzorka, korišćeno je najmanje 10 µl uzorka za analizu.

Uzorci su zasejavani na hromogeni agar UTI (engl. *urinary tract infections*) i inkubirani na 35 ± 2°C tokom 24 sata. To je podloga za identifikaciju, diferencijaciju i potvrdu kako gram-negativnih, tako i gram-pozitivnih bakterija, kao i kvasnica iz uzoraka urina. Ta podloga omogućava brzu identifikaciju gram-negativnih bakterija i nekih gram-pozitivnih bakterija na osnovu različitih boja kolonija proizvedenih reakcijom enzima specifičnih za rodove ili vrste sa dva hromogena supstrata. Karakteristične boje kolonija za svaku bakteriju su: *E. coli* - ružičaste, *Klebsiella spp*. - krupne zelene, *Proteus spp*. - mrke, roje se, *Psedomonas aeruginosa* - zelene, fluorescentne, *Enterococcus* grupa - sitne svetlo zelene boje.

Izolacija *Streptococcus spp*. i E*nterococcus spp*. vršena je na krvnom agru. Nakon zasejavanja uzoraka podloge su gajene aerobno, na tempetaruri 35-37˚C, 16-24 sata. Kolonije su sitne, sivkaste ili prozračne, konveksne i kompaktne. Na krvnom agaru streptokoki pokazuju jedan od tri tipa hemolize. Alfa – zelenkasta zona hemolize oko kolonija zbog delimične destrukcije eritrocita i parcijalne redukcije hemoglobina (do methemoglobina) u eritrocitima (*Streptococcus pneumoniae* i većina *viridans* streptokoka). Beta - prozirna zona oko kolonija zbog destrukcije eritrocita i potpune dekolorizacije hemoglobina (*Streptococcus β* hemolitičke bakterije gr. A, B, C, G). *Streptococcus agalactiae* (streptokok gr. B) ima usku zonu hemolize oko kolonije, kolonije su nešto sjajnije i nisu kompaktne. Kolonije *Enterococcus spp*. su sivkaste, sjajne i nisu kompaktne (razmazuju se ezom).

Još jedan test koji je korišćen za identifikaciji urinarnih patogena je hidroliza eskulina u 40% žuči. Zasejava se kosi eskulin-žučni agar ispitivanim sojem i inkubira preko noći na 37˚C. Ukoliko dođe do hidrolize eskulina, podloga menja boju u crnu (reakcija nastalog eskuletina sa feri-citratom u podlozi). Ovaj test je pozitivan kod enterokoka i beta-hemolitičkog streptokoka grupe D.

product. The cell wall of gram-negative bacteria is impermeable to penicillin G, so the majority of representatives are naturally resistant. However, when we speak of resistance to antimicrobial drugs, this resistance refers to the acquired resistance of microorganisms to antimicrobial agents, which they had been susceptible to before.

Antibiotic resistance may be coded by genes on the bacterial chromosome or on plasmid which is called R plasmid (4). Chromosomally encoded resistance is the result of mutation in genes for target structures (such as ribosomes, RNK polymerase, gyrase) or components of membrane that take part in the expulsion of antibiotics from the pump (pump efflux). Wide-spread forms of resistance are encoded in R plasmids and they can be exchanged by the horizontal gene transfer. Genes, whose products modify (acetylation, phosphorylation, adenylation) or dissolve drugs, or genes which encode enzymes that can prevent the adoption of antibiotics or actively expel (pump) them out, are on R plasmids. For example, some R plasmids encode ß-lactamase, enzyme that destroys ß-lactam ring, thus inducing the resistance to penicillin and cephalosporins.

Resistance to each antibiotic will develop over time. Conservative and useful application of antibiotics can prolong or even bring back the efficient clinical use of an antibiotic. A longstanding solution for antibiotic resistance requires a constant discovery and development of new drugs. After new antimicrobial agents are found and efficacy and toxicity are tested, longstanding clinical trials on people are necessary, which means that 10-25 years are needed so that an antibiotic could be used (4).

The aim of this study was the microbiological analysis of urine of infirmary patients at the Institute of Public Health during six months (1st November 2020 – 30th April 2021).

Methods

A retrospective study was conducted on the basis of obtained results of microbiological analyses that included the isolation and identification of bacterial causes of urinary tract infections and determination of their sensitivity to antibiotics with the help of antibiogram method during a six-month period (1st November 2020 – 30th April 2021). The analysis was done at the Department for Bacteriology and Parasitology at the Center for Microbiology of the Public Health Institute Kragujevac, based on the doctor's referral from the primary healthcare – Health Center Kragujevac.

A positive result means that bacterial pathogens were found in significant numbers in the patient's urine sample. A significant number of bacteria in urine is the number of bacteria > 100,000 CFU/ml (colony forming units per milliliter) in the midstream sample of urine, which is deemed to be the criterion necessary for the confirmation of bacterial infection. A smaller number than that one is deemed to be contamination. After an adequate sample collection, at least 10 µl of the sample was used for the analysis.

The samples were inoculated on chromogenic UTI agar and incubated at 35 ± 2˚C during 24 hours. That was the medium for the identification, differentiation and confirmation of gram-negative and gram-positive bacteria, as well as of fungi from urine samples. That medium enabled the fast identification of gram-negative bacteria and some gram-positive bacteria according to different colors of colonies produced by the reaction of enzymes specific for the species with two chromogenic substrates. Characteristic colors of colonies for each bacterium are the following: *E. coli* – pink, *Klebsiella spp.* – big green, *Proteus spp.* – dark, swarming, *Psedomonas aeruginosa* – green, fluorescent, *Enterococcus* group – tiny light green.

Streptococcus spp. and *Enterococcus spp.* were isolated on blood agar. After samples were inoculated, media were grown aerobically at 35-37˚C, 16-24 hours. Colonies were small, grayish or translucent, convex and compact. *Streptococci* show one of three types of hemolysis on blood agar. Alpha – green zone of hemolysis around colonies due to the partial reduction of erythrocytes and partial reduction of hemoglobin (to methemoglobin) in erythrocytes (*Streptococcus pneumoniae* and most of *viridians streptococci*). Beta - translucent zone around colonies due to the destruction of erythrocytes and complete decolorization of hemoglobin (*Streptococcus ß* hemolytic bacteria gr. A, B, C, G). *Streptococcus agalactiae* (*streptococcus group B*) had a narrow zone of hemolysis around the colony, colonies were a little bit shinier and not compact. Colonies *Enterococcus spp.* were grayish, shiny and not compact (they were stained using esis).

Za izolaciju i identifikaciju enterobakterija se koristila diferencijalna podloga endo agar. Zasejani uzorci se inkubiraju aerobno, na temperaturi 35-37˚C, 16-24 sata. Identifikacija enterobakterija primarno se zasniva na ispitivanju biohemijskih osobina. U rutinskoj dijagnostici koristi se klasični biohemijski niz za ispitivanje biohemijskih osobina: *Kligler*-ov trostruki ili dvostruki šećer (ispitivanje sposobnosti fermentacije šećera laktoze i dekstroze, kao i redukcije sumpora, tj. stvaranja vodonik sulfida); peptonska voda za dokazivanje indola (ispitivanje sposobnosti razgradnje triptofana); metil red - *Voges Proskauer* (ispitivanje produkata fermentacije glukoze); *Simons* citratni agar (ispitivanje sposobnosti korišćenja citrata); ureaza test (ispitivanje sposobnosti razgradnje uree).

Za identifikaciju gram negativnih nefermentujućih bacila (*Pseudomonas spp*., *Acinetobacter spp*. i dr.) uglavnom se koristi CHROM agar, na kome daju karakterističnu boju kolonije: *Pseudomonas aeruginosa* – zelene, fluorescentne; *Acinetobacter* - zelene, sitnije, sjajne kolonije. Inače, bakterije rastu aerobno, na temperaturi 35-37˚C, 16-24 sata. Za identifikaciju koriste se sledeće osobine: nereaktivnost na *Kligler*-ovom dvostrukom/trostrukom šećeru; preparat sa kulture - gram negativni bacili, kokobacili; oksidaza reakcija (5).

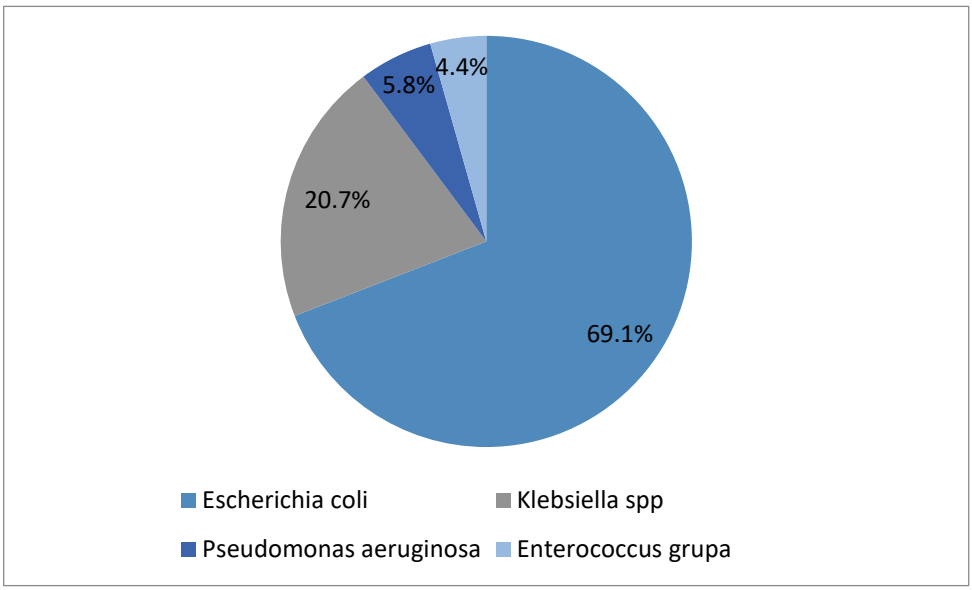
Ispitivanje osetljivosti na antibiotike je sprovedeno disk-difuzionom metodom na *Mueller-Hinton* agaru (antibiogram metoda). Bakterijski inokulum se priprema razblaživanjem 18-24 časovne čiste bakterijske kulture. Ezom se pikira 4-5 kolonija i prenese u 3 ml fiziološkog rastvora. Suspenzija se vorteksira, a potom se gustina suspenzije podešava poređenjem sa *McFarland* standardom 0,5 za turbiditet. Inokulum se zasejava ravnomerno na površinu podloge. Posle zasejavanja inokuluma poželjno je da podloga stoji 10-15 minuta na sobnoj temperaturi da bi se površina osušila (5,6).

Postavljanje antibiogram tableta ili diskova se izvodi dispenzerom ili sterilnom pincetom. Razmak između diskova je najmanje 1,7-2 cm, a rastojanje od ivice petri šolje najmanje 1 cm. Na ploču prečnika 9 cm nanosi se maksimalno 6 diskova, a na ploču prečnika 12 cm maksimalno 8 diskova. Zone inhibicije rasta očitavane su prema preporukama *Eucast*-a (engl. *European Committee on Antimicrobial Susceptibility Testing*). Ispitivana je osetljivost na: cefaleksin, ceftriakson, amikacin, gentamicin, ciprofloksacin, fosfomicin, meropenem, ceftazidim, piperacilin tazobaktam, ampicilin i norfloksacin. Test osetljivosti je interpretiran prema kriterijumima koje je objavio *Eucast* (7).

Analiza svih prikupljenih uzoraka urina u navedenom šestomesečnom period vršena je primenom deskriptivne statistike.

Rezultati

Od svih testiranih uzoraka pozitivno na patogene mikroorganizme je bilo 1.218 (25,3%). Najzastupljeniji patogeni urinarnog trakta u ispitivanom periodu bili su: *Escherichia coli* 842 (69,1%), *Klebsiella spp*. 252 (20,7%), *Pseudomonas aeruginosa* 71 (5,8%) i *Enterococcus* grupa 53 (4,4%) (grafikon 1).



Grafikon 1. Procentualno učešće pojedinih uzročnika urinarnih infekcija među svim identifikovanim prouzrokovačima u urinu ambulantnih pacijenata Instituta za javno zdravlje Kragujevac

One more test that was used for the identification of urinary pathogens was hydrolysis of esculin in 40% bile. Bile esculin agar is inoculated with the examined strain and incubated at 37˚C at night. If it comes to esculin hydrolysis, the medium changes its color into black (reaction of esculin with ferric-citrate in the medium). This test is positive in *enterococcus* and beta-hemolytic *streptococcus* group D.

A differential medium endo agar was used for the isolation and identification of *Enterobacteriaceae*. Inoculated samples are incubated aerobically, at 35-37˚C, 16 to 24 hours. The identification of *Enterobacteriaceae* is primarily based on the examination of biochemical properties. Classical biochemical series is used in routine diagnostics for the examination of biochemical properties: Kligler's triple or double sugar test (examination of the ability of fermentation of lactose and dextrose , as well as the reduction of sulfur, that is, the creation of hydrogen-sulfide); peptone water for the detection of indole (test the ability of tryptophan dissolution); methyl red – *Voges-Proskauer* (test the products of glucose fermentation); Simmons citrate agar (test the ability to utilize citrate); urease test (test the ability to split urea).

CHROM agar is mainly used for the identification of gram-negative non-fermenting germs (*Pseudomonas spp.*, *Acinetobacter spp.*, etc.), and characteristic color is shown for the following colonies: *Pseudomonas aeruginosa* – green, fluorescent; *Acinetobacter* – green, smaller, shiny colonies. However, bacteria grow aerobically, at 35-37˚C, 16-24 hours. The following characteristics are used for the identification: non-fermentation on Kligler double/triple sugar; preparation of the culture – gram-negative bacteria, coccobacilli; oxidase reaction (5).

Disc-diffusion method on Mueller-Hinton agar (antibiogram method) is used to test resistance to antibiotics. Bacterial inoculum is prepared by diluting the clean bacterial culture. Four-five colonies are picked with esis and transferred to 3 ml of physiological solution. The suspension is vortexed, and then density of the suspension is adjusted by comparing it with McFarland standard 0.5 for turbidity. Inoculum is inoculated equally on the surface of the medium. After it is inoculated, the medium should remain 10-15 minutes at room temperature so that the surface would dry (5,6).

Antibiogram tablets or discs are placed with the help of dispenser or sterile tweezers. The distance between discs is at least 1.7-2 cm, while the distance from the edge of Petri mug is at least 1 cm. Maximum 6 discs can be put on a 9 cm diameter Petri dish plate, and maximum 8 discs on 12 cm diameter plate. Zones of the inhibition of growth were read according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (Eucast). Susceptibility to following drugs was tested: cephalexin, ceftriaxone, amikacin, gentamicin, ciprofloxacin, fosfomycin, meropenem, ceftazidime, piperacillin tazobactam,

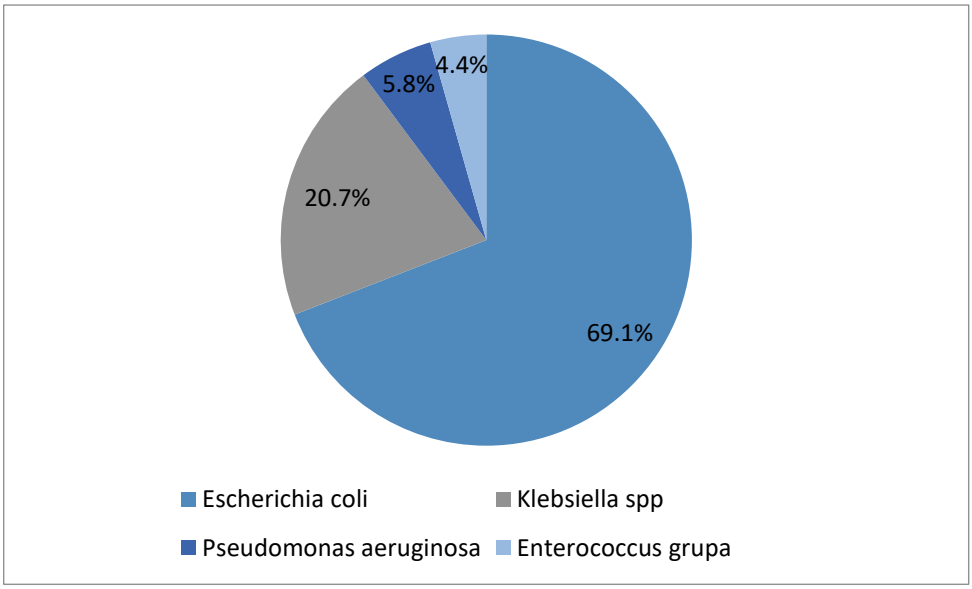


Figure 1. Percentage share of individual causes of urinary tract infections among all identified causative agents in the urine of the Institute of Public Health Kragujevac

Tabela 1. Distribucija izolovanih uzročnika urinarnih infekcija prema polu ispitanika, Institut za javno zdravlje Kragujevac

Vrsta uzročnika	***Escherichia coli***		***Klebsiella spp.***		***Pseudomonas aeruginosa***		***Enterococcus* grupa**	
Ukupno	**842 (100%)**		**252 (100%)**		**71 (100%)**		**53 (100%)**	
Pol	Muškarci	Žene	Muškarci	Žene	Muškarci	Žene	Muškarci	Žene
Broj (%)	146 (17,3)	696 (82,7)	130 (51,6)	122 (48,4)	54 (76,1)	17 (23,9)	26 (49,1)	27 (50,9)

Bakterija *E. coli* je bila češća kod žena (82,7%), a *Pseudomonas aeruginosa* kod muškaraca (76,1%). *Klebsiella spp*. i *Enterococcus spp*. su se skoro podjednako javljale kod oba pola (tabela 1).

Osetljivost je testirana na antibiotike iz grupa cefalosporina, aminoglikozida, karbapenema, penicilina, kao i na hemioterapeutike iz grupe fluorohinolona i na fosfomicin (ukoliko je broj izolovanih patogena bio manji od 100.000 nije rađena antibiogram metoda).

Izolovani patogeni (osim predstavnika *Enterococcus spp*.) su testirani na cefaleksin, ceftriakson i ceftazidim koji spadaju u grupu cefalosporina, a dobijeni rezultati su prikazani u tabeli 2. Kada se analizira grupna osetljivost prema svim testiranim antibioticima iz grupe cefalosporina, uočava se da je najosetljivija bakterija bila E. coli, a najrezistentnija *P. aeruginosa*. Dok se ozbiljna analiza rezistencije na ceftazidim ne može vršiti zbog veoma malog testiranog uzorka, preostala dva antibiotika su delovala prema sledećem obrascu: (1) Ceftriakson je bio najdelotvorniji prema *E. coli* (čak 88,3% senzitivnih izolata), dok je njegova delotvornost bila značajno manja prema *Klebsiella spp.* (51,8% osetljivih sojeva) i naročito prema *P. aeruginosa* (20,3% osetljivosti). Cefaleksin je bio nešto manje aktivan, ali je osetljivost izolata i u ovom slučaju mogla da se poređa u sledeći opadajući niz: E. coli (75,5%), *Klebsiella spp*. (33,1%) i *P. aeruginosa* (samo 4,3% osetljivosti).

Kada je testirana efikasnost aminoglikozida, uočena je takođe velika osetljivost *E. coli*, za kojom slede *Klebsiella spp*., *P. aeruginosa* i *Enterococcus spp.* (tabela 3). Iz grupe aminoglikozida na amikacin su bile senzitivne, u najvećem broju slučajeva bakterije *E. coli* (čak 96%), zatim slede *Klebsiella*

Tabela 2. Osetljivost izolovanih patogena na antibiotike iz grupe cefalosporina

Patogeni uzročnici	***Escherichia coli***		***Klebsiella spp.***		***Pseudomonas aeruginosa***	
Vrsta antibiotika	**S Broj (%)**	**R Broj (%)**	**S Broj (%)**	**R Broj (%)**	**S Broj (%)**	**R Broj (%)**
Cefaleksin	628 (75,5)	204 (24,5)	84 (33,1)	168 (66,6)	3 (4,3)	67 (95,7)
Ceftriakson	743 (88,3)	98 (11,7)	130 (51,8)	121 (48,2)	14 (20,3)	55 (79,7)
Ceftazidim	1 (50)	1 (50)	5 (55,6)	4 (44,4)	25 (44,6)	31 (55,4)

S-senzitivni, R-rezistentni izolati

Tabela 3. Osetljivost izolovanih patogena na antibiotike iz grupe aminoglikozida

Patogeni uzročnici	***Escherichia coli***		***Klebsiella spp.***		***Pseudomonas aeruginosa***		***Enterococcus* grupa**	
Vrsta antibiotika	**S Broj (%)**	**R Broj (%)**	**S Broj (%)**	**R Broj (%)**	**S Broj (%)**	**R Broj (%)**	**S Broj (%)**	**R Broj (%)**
Gentamicin	665 (79,3)	174 (20,7)	133 (52,8)	119 (47,2)	28 (40,0)	42 (60,0)	13 (25,5)	38 (74,5)
Amikacin	806 (96,0)	33 (4,0)	187 (74,8)	63 (25,2)	46 (69,7)	20 (30,0)	nt	nt

S-senzitivni, R-rezistentni izolati, nt-nije testirano

Table 1. Sex-specific distribution of isolated causes of urinary tract infections, Institute of Public Health Kragujevac

Type of causative agent	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* grupa	
Total	**842 (100%)**		**252 (100%)**		**71 (100%)**		**53 (100%)**	
Gender	Men	Women	Men	Women	Men	Women	Men	Women
Number (%)	146 (17.3)	696 (82.7)	130 (51.6)	122 (48.4)	54 (76.1)	17 (23.9)	26 (49.1)	27 (50.9)

ampicillin and norfloxacin. Susceptibility test was interpreted according to the criteria published by Eucast (7).

The analysis of all collected urine samples in the given time period was done with the help of descriptive statistics.

Results

Of all tested samples, 1218 were positive to pathogenic microorganisms (25.3%). The most common urinary tract pathogens in the examined period were the following: *Escherichia coli* 842 (69.1%), *Klebsiella spp.* 252 (20.7%), *Pseudomonas aeruginosa* 71 (5.8%) and *Enterococcus* group 53 (4.4%) (Figure 1).

E. coli was more frequent in women (82.7%), while *Pseudomonas aeruginosa* was more frequent in men (76.1%). *Klebsiella spp.* and *Enterococcus spp.* appeared almost equally in both men and women (Table 1).

Susceptibility was tested for antibiotics from the group of cephalosporins, amino-glycosides, carbapenem, penicillin, as well as for chemotherapeutics from the group of fluoroquinolones and fosfomycin (if the number of isolated pathogens was less than 100,000, antibiogram method was not done). Isolated pathogens (except the representatives of *Enterococcus spp.*) were tested for susceptibility to cephalexin, ceftriaxone and ceftazidime that belong to the group of cephalosporins, and the obtained results were presented in Table 2.

When group susceptibility to all tested antibiotics from the group of cephalosporins is analyzed, bacterium *E. coli* is found to be the most susceptible, while *P. aeruginosa* is the most

Table 2. Susceptibility of isolated pathogens to cephalosporin antibiotics

Pathogenic causes	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*	
Types of antibiotics	**S Number (%)**	**R Number (%)**	**S Number (%)**	**R Number (%)**	**S Number (%)**	**R Number (%)**
Cefalexin	628 (75.5)	204 (24.5)	84 (33.1)	168 (66.6)	3 (4.3)	67 (95.7)
Ceftriaxon	743 (88.3)	98 (11.7)	130 (51.8)	121 (48.2)	14 (20.3)	55 (79.7)
Ceftazidim	1 (50)	1 (50)	5 (55.6)	4 (44.4)	25 (44.6)	31 (55.4)

S-sensitive, R-resistant isolates

Table 3. Susceptibility of isolated pathogens to antibiotics from the group of aminoglycosides

Pathogenic causes	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* group	
Types of antibiotics	**S N (%)**	**R N (%)**	**S N (%)**	**R N (%)**	**S N (%)**	**R N (%)**	**S N (%)**	**R N (%)**
Gentamycin	665 (79.3)	174 (20.7)	133 (52.8)	119 (47.2)	28 (40.0)	42 (60.0)	13 (25.5)	38 (74.5)
Amikacin	806 (96.0)	33 (4.0)	187 (74.8)	63 (25.2)	46 (69.7)	20 (30.0)	nt	nt

S-sensitive, R-resistant isolates, nt- not tested

Tabela 4. Osetljivost izolovanih patogena na antibiotike iz grupe fluorohinolona

Patogeni uzročnici	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* grupa	
Vrsta antibiotika	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)
Ciprofloksacin	542 (64,5)	298 (35,5)	115 (45,8)	136 (54,2)	24 (36,4)	42 (63,6)	28 (53,8)	24 (46,2)
Norfloksacin	nt	nt	nt	nt	nt	nt	3 (33,3)	6 (66,7)

S-senzitivni, R-rezistentni izolati, nt-nije testirano

Tabela 5. Osetljivost izolovanih patogena na antibiotike iz grupe karbapanema

Patogeni uzročnici	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* grupa	
Vrsta antibiotika	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)
Meropenem	8 (88,9)	1(11,1)	39 (100,0)	nt	45 (78,9)	12(21,1)	28 (53,8)	24 (46,2)

S-senzitivni, R-rezistentni izolati, nt-nije testirano

spp. i *P. aeruginosa*, sa približnim procentom osetljivih sojeva (74,8% i 69,7%), dok bakterije iz *Enterococcus* grupe nisu testirane na ovaj antibiotik. Slična je situacija i sa gentamicinom, s tim da su na njega testirani i izolati *Enterococcus spp*., ali je samo manji procenat (25,5%) bio senzitivan.

Iz grupe fluorohinolona svi izolati su testirani na ciprofloksacin (tabela 4). Određeni broj svih izolovanih patogena je bio senzitivan na ciprofloksacin, pri čemu je najveći procenat bio zastupljen kod bakterije *E. coli* (64,5%). Slede bakterije *Enterococcus* grupe (53,8%), *Klebsiella spp*. (45,8%) i *P. aeruginosa* (36,4%). Na norfloksacin su testirane jedino bakterije iz *Enterococcus* grupe i mali broj nalaza je bio senzitivan na ovaj antibiotik, s tim da je i ukupan broj testiranih izolata bio mali.

Iz grupe karbapenema izolovani patogeni, sem bakterija iz *Enterococcus* grupe, su testirani na antibiotik meropenem (tabela 5). Ovde su svi testirani izolati *Klebsiella spp*. (ukupno 39) svi bili osetljivi, dok je procenat osetljivosti bio nešto manji u slučaju *E. coli* (88,9%) i *P. aeruginosa* (78,9%). Treba samo istaći da je senzitivnost *E. coli* testirana prema malom broju izolata.

Tabela 6. Osetljivost izolovanih patogena na antibiotike iz grupe penicilina

Patogeni uzročnici	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* grupa	
Vrsta antibiotika	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)
Piperacilin tazobaktam	1 (50,0)	1 (50,0)	6 (85,7)	1 (14,3)	43 (81,1)	10 (18,9)	nt	nt
Ampicilin	nt	nt	nt	nt	nt	nt	6 (11,8)	45 (88,2)

S-senzitivni, R-rezistentni izolati, nt-nije testirano

Tabela 7. Osetljivost izolovanih patogena na antibiotike iz grupe uroantiseptika

Patogeni uzročnici	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* grupa	
Vrsta antibiotika	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)	S Broj (%)	R Broj (%)
Fosfomicin	243 (93,8)	16 (6,2)	54 (65,8)	28 (34,2)	2 (16,7)	10 (83,3)	6 (11,8)	45 (88,2)

S-senzitivni, R-rezistentni izolati

Table 4. Susceptibility of isolated pathogens to fluoroquinolone antibiotics

Pathogenic causes	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* group	
Types of antibiotics	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)
Ciprofloxacin	542 (64.5)	298 (35.5)	115 (45.8)	136 (54.2)	24 (36.4)	42 (63.6)	28 (53.8)	24 (46.2)
Norfloxacin	nt	nt	nt	nt	nt	nt	3 (33.3)	6 (66.7)

S-sensitive, R-resistant isolates, nt- not tested

Table 5. Susceptibility of isolated pathogens to carbapanem antibiotics

Pathogenic causes	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* group	
Types of antibiotics	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)
Meropenem	8 (88.9)	1(11.1)	39 (100.0)	nt	45 (78.9)	12(21.1)	28 (53.8)	24 (46.2)

S-sensitive, R-resistant isolates, nt- not tested

resistant. While a serious analysis of resistance to ceftazidime cannot be done due to a very small tested sample, the remaining two antibiotics acted according to the following pattern: (1) Ceftriaxone is the most efficient for *E. coli* (even 88.3% of sensitive isolates), while its efficacy is significantly smaller for *Klebsiella spp.* (51.8% of sensitive strains) and especially for *P. aeruginosa* (20.3% of sensitivity). Cephalexin was somewhat less active, but the sensitivity of the isolate in this case could be placed in the following decreasing sequence: *E. coli* (75.5%), *Klebsiella spp.* (33.1%) and *P. aeruginosa* (only 4.3% of sensitivity).

When the efficiency of aminoglycosides was tested, high sensitivity of *E. coli* was observed, and then of *Klebsiella spp.*, *P. aeruginosa* and *Enterococcus spp.* (Table 3). From the group of aminoglycosides, in most cases bacteria *E. coli* was sensitive to amikacin (even 96%), followed by *Klebsiella spp.* and *P. aeruginosa*, with the similar percentage of sensitive strains (74.8% and 69.7%), while bacteria from the *Enterococcus* group were not tested for susceptibility to these antibiotics. Similar results were obtained for gentamicin,

Table 6. Susceptibility of isolated pathogens to penicillin antibiotics

Patogeni uzročnici	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* group	
Vrsta antibiotika	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)
Piperacillin tazobactam	1 (50.0)	1 (50.0)	6 (85.7)	1 (14.3)	43 (81.1)	10 (18.9)	nt	nt
Ampicillin	nt	nt	nt	nt	nt	nt	6 (11.8)	45 (88.2)

S-sensitive, R-resistant isolates, nt- not tested

Table 7. Susceptibility of isolated pathogens to uroantiseptic

Pathogenic causes	*Escherichia coli*		*Klebsiella spp.*		*Pseudomonas aeruginosa*		*Enterococcus* group	
Types of antibiotics	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)	S N (%)	R N (%)
Fosfomycin	243 (93.8)	16 (6.2)	54 (65.8)	28 (34.2)	2 (16.7)	10 (83.3)	6 (11.8)	45 (88.2)

S-sensitive, R-resistant isolates

Iz grupe penicilina testirani antibiotici su: piperacilin tazobaktam (prema malom broju *E. coli* i *Klebsiella spp*. izolata, i nešto većem broju izolata *P. aeruginosa*) i ampicilin (prema *Enterococcus spp*.) (tabela 6). Procentualno gledano, *Klebsiella spp*. je bila najsenzitivnija (85,7%), a zatim bakterije *P. aeruginosa* (81,1%), na piperacilin tazobaktam. S druge strane, bakterije iz *Enterococcus* grupe, testirane samo na ampicilin, bile su senzitivne u malom broju uzoraka (11,8%).

Iz grupe uroantiseptika primenjen je fosfomicin, a testirani su svi patogeni sem bakterija iz *Enterococcus* grupe. Bakterija *E. coli* i u manjem procentu *Klebsiella spp*. su pokazale osetljivost, dok je bakterija *P. aeruginosa* bila pretežno rezistentna (Tabela 7).

Diskusija

Urinarna infekcija je čest problem svuda u svetu, češće kod osoba ženskog pola u svim uzrastima (1). S obzirom na to da uropatogeni poseduju mehanizme za razvoj rezistencije, potrebno je u terapiji koristiti antibiotike u zavisnosti od rezultata antibiograma. Uglavnom, preko 90% svih izolata su gram negativni patogeni (8-10). Kao što se i očekivalo, u našem istraživanju *E. coli* je bila najčešći izolat i češće je izazivala urinarne tegobe kod osoba ženskog pola. To je ujedno bio i najčešći patogen povezan sa infekcijama urogenitalnog trakta detektovan i u drugim studijama (1-4). *E. coli* generalno pripada normalnoj flori debelog creva čoveka i zbog toga može lako kolonizovati urinarni trakt. Ostali gram-negativni patogeni koji se mogu naći u urinu, iako su prisutni u manjim procentima, igraju značajnu ulogu u urinarnim infekcijama zbog svoje patogenosti i visoke otpornosti na antibiotike. Zapravo, šestomesečni presek je pokazao uropatološki status populacije na nivou jednog grada. Pokazali smo da su, pored *E. coli*, ostali uropatogeni bili *Klebsiella spp.*, *Enterococcus spp.* i *Pseudomonas aeruginosa*.

Naši rezultati su uporedivi sa rezultatima studije Đorđević i sar., koji su analizirali učestalost vanbolničkih infekcija urinarnog trakta (2). Najčešće izolovani uzročnici urinarnih infekcija kod njih su bili *E. coli* (56,6%), zatim redom vrste *Klebsiella spp.* (16,2%), *Proteus spp.* (14,68%), *Enterococcus spp.* (5,3%) i *P. aeruginosa* (3,7%). Drugim rečima, procentualna zastupljenost patogena je opadala u sličnom nizu kao i u našoj studiji (*E. coli*, *Klebsiella spp.*, *P. aeruginosa*, *Enterococcus spp.*), s tim da su oni uočili i značajno prisustvo *Proteus spp.* Što se tiče distribucije patogena po polovima, sličnost pomenute i naše studije se uočava u slučaju *E. coli*, koja je mnogo češće izazivala infekcije kod žena svih starosnih grupa (oko 70%) (2).

Afinitet uropatogena prema polu određen je pre svega anatomsko-fiziološkim karakteristikama pola. Ovo bi mogli objasniti činjenicom da osobe ženskog pola se češće javljaju doktoru kada sumnjaju na urinarnu infekciju, mada se to sa sigurnošću ne može potvrditi. Podaci prikazani u ovom radu govore da je kod ženskog pola znatno zastupljeniji uropatogen *E. coli.* Sa druge strane, *P. aeruginosa* je prisutnija kod muškog pola, dok su se *Klebsiella spp.* i *Enterococcus spp.* pojavljivale u urinu oba pola u približno jednakom broju. U skladu sa ovim su i literaturni podaci koji ukazuju da su učestaliji uzročnici infekcija urinarnog trakta kod muškog pola bile *Klebsiella spp.*, *Proteus spp.*, *Pseudomonas spp.* i *Acinetobacter spp.* (1,12).

U prošlosti, porast rezistencije uropatogena bio je mnogo veći problem bolničkih sredina. Međutim, novije studije pokazuju da je porast rezistentnih sojeva prisutan i u opštoj populaciji (3). Iz ovog razloga treba biti obazriv prilikom propisivanja terapije, naročito ako se radi o starijim osobama, osobama s hroničnim oboljenjima, ili osobama s malformacijama urinarnog trakta. Tada se naročito preporučuje propisivanje terapije po antibiogramu (4). Podaci naše studije pokazuju da je rezistencija bila najmanje zastupljena kod izolata *E. coli*, a najčešća kod *P. aeruginosa* i *Enterococcus spp.*. Imajući u vidu da obe bakterije nose R plazmide koji im pružaju multiplu rezistenciju prema većem broju antibiotika (4,11), kao i činjenicu da je multipla rezistencija kod enterokoka u značajnom porastu (13), ovaj rezultat ne iznenađuje.

Iako je studija obuhvatila relativno mali uzorak izolata urogenitalnih patogena, naročito *Enterococcus spp.* i *P. aeruginosa*, ako se uzmu u obzir i veličina testiranog uzorka i procenti rezistencije, lekovi prvog izbora u terapiji urinarnih infekcija bi bili sledeći: za *E. coli* amikacin (aminoglikozid) i fosfomicin, donekle i ceftriakson (cefalosporin), a za *Klebsiella spp.* meropenem (karbapenem) i takođe amikacin. Što se tiče *P. aeruginosa*, najefikasnijim su se pokazali takođe meropenem, kao i penicilinski antibiotik piperacilin-tazobaktam. Konačno, na osnovu dobijenih rezultata ne može se preporučiti nijedan od testiranih antibiotika kao terapija infekcija bakterijama *Enterococcus spp.*, s

however, isolates of *Enterococcus spp.* were also tested, and only a small percentage (25.5%) was sensitive.

From the group of fluoroquinolones, all isolates were tested for susceptibility to ciprofloxacin (Table 4). A certain number of isolated pathogens were sensitive to ciprofloxacin, while the greatest percentage was in bacteria *E. coli* (64.5%), followed by *Enterococci* (53.8%), *Klebsiella spp.* (45.8%) and *P. aeruginosa* (36.4%). Bacteria from the *Enterococcus* group were tested for susceptibility to norfloxacin, and a small number of results were sensitive to it, although the total number of tested isolates was small.

From the group of carbapenem, all isolated pathogens, except bacteria from *Enterococcus* group, were tested for susceptibility to meropenem (Table 5). Here of all tested *Klebsiella spp.* isolates (total 39), all were sensitive, while the percentage of susceptibility was a little bit smaller in case of *E. coli* (88.9%) and *P. aeruginosa* (78.9%). It should be emphasized that the sensitivity of *E. coli* was tested according to a small number of isolates.

As far as penicillin is concerned, the following antibiotics were tested: piperacillin tazobactam (according to the small number of *E. coli* and *Klebsiella spp.* isolates, and somewhat larger number of *P. aeruginosa* isolates) and ampicillin (*Enterococcus spp.*) (Table 6). In percentages, *Klebsiella spp.* was the most sensitive (85.7%), and then bacteria *P. aeruginosa* (81.1%) to piperacillin tazobactam. On the other hand, bacteria from *Enterococcus* group were tested only for susceptibility to ampicillin, and they were sensitive in a small number of samples (11.8%).

From the group of uroantiseptics, fosfomycin was applied, and all pathogens were tested except bacteria from *Enterococcus* group. Bacteria *E. coli* and *Klebsiella spp.* in smaller percentages showed sensitivity, while *P. aeruginosa* was dominantly resistant (Table 7).

Discussion

Urinary tract infections are a common problem worldwide, and they appear more frequently in women of all ages (1). Considering the fact that urinary pathogens possess mechanisms for the development of resistance, antibiotics should be used according to the antibiogram. More than 90% of all isolates are mainly gram-negative pathogens (8-10). As it had been expected, in our study *E. coli* was the most frequent isolate and it caused urinary tract problems more frequently in females. At the same time, it was the most frequent pathogen connected with the infections of urogenital tract that was detected in other studies, as well (1-4). *E. coli* generally belongs to the normal intestinal microflora and therefore, it can easily colonize the urinary tract. Other gram-negative pathogens that can be found in urine, although they are present in small percentages, have a significant role in urinary tract infections due to their pathogenicity and high resistance to antibiotics. Actually, the six months analysis showed the uropathological status of population at the level of one city. We showed that, in addition to *E.coli*, other uropathogens were *Klebsiella spp.*, *Enterococcus spp.* and *Pseudomonas aeruginosa*.

Our results are comparable to the results of a study of Djordjevic and associates, who analyzed the frequency of out-patient urinary tract infections (2). The most frequently isolated causes of urinary tract infections in their study were *E. coli* (56.6%), and then *Klebsiella spp.* (16.2%), *Proteus spp.* (14.68%), *Enterococcus spp.* (5.3%) and *P. aeruginosa* (3.7%). In other words, percentage of pathogens decreased in a similar sequence as in our study (*E. coli*, *Klebsiella spp.*, *P. aeruginosa*, *Enterococcus spp.*), but they noted a significant presence of *Proteus spp.* As far as distribution of pathogens by gender is concerned, the similarity between the above mentioned and our study is noticed in case of *E. coli*, which caused infections more frequently in women of all ages (about 70%) (2).

The affinity of uropathogens with gender was determined, first of all, by anatomical-physiological characteristics of gender. This could be explained by the fact that women more frequently visit their doctors when they suspect that they have a urinary infection, although this cannot be confirmed with certainty. Data shown in this paper indicate that uropathogen *E. coli* is more present in women. On the other hand, *P. aeruginosa* is more present in males, while *Klebsiella spp.* and *Enterococcus spp.* appeared in urine of both men and women in almost equal numbers. Literature data are in accordance with this, and they indicate that more frequent causes of urinary tract infections in males were *Klebsiella spp.*, *Proteus spp.*, *Pseudomonas spp.* and *Acinetobacter spp.* (1,12).

In the past, the increase in the resistance of uropathogens was a great problem in the hospital

obzirom na to da je i brojnost testiranih izolata bila mala, ali i rezistencija među testiranim izolatima visoka. Interesantno je da su uropatogeni uglavnom bili otporni na antibiotike iz grupe penicilina, što se razlikuje od nekih dostupnih literaturnih podataka. Naime, ranija studija pokazuje da su sojevi enterokoka pokazali izrazitu osetljivost na ampicilin i penicilin, što se razlikuje od rezultata našeg istraživanja (1,14).

Zaključak

Institutu za javno zdravlje Kragujevac, koji predstavlja jedinu zdravstvenu ustanovu tog tipa u Šumadijskom okrugu, u periodu od novembra 2020. do aprila 2021. godine, od 4.809 uzoraka urina, 1218 je bilo pozitivno na uropatogene mikroorganizme. Češće su bili izolovani Gram-negativni uropatogeni od Gram-pozitivnih, a bakterija *Escherichia coli* je bila najčešća među njima. Žene su bile češće sa urinarnom infekcijom uzrokovanom *E. coli*, a osobe muškog pola bakterijom P. aeruginosa. Infekcije *E. coli* su se u najvećem procentu mogu lečiti amikacinom i fosfomicinom, a *Klebsiella spp.* amikacinom i meropenemom. Najpouzdaniji način definisanja pravilne antibiotske terapije upravo predstavlja izolacija i identifikacija uzročnika, a zatim testiranje osetljivosti konkretnog izolata metodom antibiograma.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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environment. However, recent studies have shown that the increase in resistant strains is present in general population, as well (3). Due to this reason, one should be careful when prescribing therapy, especially in older persons, persons with chronic diseases, or persons with urinary tract malformations. Then, therapy is prescribed according to the antibiogram (4). Data from our study show that resistance was least present in *E. coli* isolates, while it was most frequent in *P. aeruginosa* and *Enterococcus spp.* Having in mind that both bacteria have R plasmids that provide multiple resistance to a great number of antibiotics (4,11), as well as the fact that multiple resistance in *Enterococci* is significantly increasing (13), this result is not surprising.

Although the study included a relatively small number of isolates of urogenital pathogens, especially *Enterococcus spp.* and *P. aeruginosa*, and if we take into account the size of the tested sample and the percentages of resistance, first choice drugs for the treatment of urinary tract infections would be the following: for *E. coli* amikacin (aminoglycoside) and fosfomycin, partly ceftriaxone (cephalosporin), and for *Klebsiella spp.* meropenem (carbapenem) and also amikacin. As far as *P. aeruginosa* is concerned, meropenem was shown to be the most efficient, as well as penicillin antibiotic piperacillin-tazobactam. Finally, according to the obtained results, there are no antibiotics that can be recommended as the therapy for infections caused by bacteria *Enterococcus spp.*, considering that the number of tested isolates was small, and resistance among the tested isolates high. It is interesting that uropathogens are mainly resistant to penicillin antibiotics, which is contrary to some available literature data. Namely, the previous study has shown that enterococci strains show high sensitivity to ampicillin and penicillin, which is contrary to the results of our research.

Conclusion

Of 4809 urine samples, 1219 were positive to uropathogenic microorganisms at the Institute of Public Health Kragujevac, which is the only health care institution of that kind in Sumadija county from November 2020 to April 2021. Gram-negative pathogens were isolated more frequently than gram-positive, while *Escherichia coli* was the most frequent among them. Women had more frequently the urinary tract infections caused by *E. coli*, while men had more frequently infections caused by *P. aeruginosa*. *E. coli* infections can be treated with amikacin and fosfomycin in most cases, while *Klebsiella spp.* with amikacin and meropenem. The most reliable way of defining the correct antibiotic therapy is precisely the isolation and identification of causative agents, and then testing the sensitivity of particular isolate with the help of antibiogram method.

Competing interests

The author declares no competing interests.

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