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CIPROFLOKSACIN REZISTENTNA *NEISSERIA GONORRHOEAE* KOD MUŠKARACA SA GONOROIČNIM URETRITISOM LEČENIH U GRADSKOM ZAVODU ZA KOŽNE I VENERIČNE BOLESTI U BEOGRADU

Milan Bjekić[1], Tatjana Bojović Aleksić[2], Maja Vivoda[2]
[1]Gradski zavod za kožne i venerične bolesti, Beograd, Srbija
[2]Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut", Beograd, Srbija
Autor za korespondenciju: Milan Bjekić, Gradski zavod za kožne i venerične bolesti, Džordža Vašingtona 17, 11000 Beograd, Srbija; e-mail: milinkovski@gmail.com

SAŽETAK

Uvod/cilj: Gonoreja je akutna polno prenosiva infekcija koju izaziva *Neisseria gonorrhoeae* (NG) i koja zahvata cilindrični i prelazni epitel uretre, cerviksa, rektuma i farinksa. U poslednjoj deceniji u zemljama Evropske unije došlo je do porasta rezistencije NG na antibiotike iz grupe makrolida, tetraciklina i hinolona, dok je rezistencija na ceftriakson bila izuzetno retka. Cilj ovog rada bio je da se utvrde učestalost sojeva NG rezistentnih na ciprofloksacin kod pacijenata lečenih zbog gonoroičnog uretritisa i karakteristike obolelih od gonoreje u odnosu na antimikrobnu rezistenciju.
Metode: U istraživanje je uključeno 55 muškaraca koji su se javili na pregled dermatologu zbog gnojnog iscetka iz uretre. Podaci o uzrastu pacijenata, seksualnoj orijentaciji, prethodnom obolevanju od gonoreje i HIV statusu preuzeti su iz medicinskih kartona obolelih od gonoreje. Klinički uzorci za kultivaciju NG prikupljeni su odgovarajućim brisevima, koji su inokulisani na selektivnu i neselektivnu hranljivu podlogu i inkubirani u vlažnoj sredini sa 5% CO_2 na 37°C, 18-24 h. Oksidaza-pozitivne kolonije su ispitivane MALDI-TOF MS (*Matrix-Assisted Laser Desorption Ionization Time-of-Flight*) sistemom, čime je potvrđena identifikacija NG. Ispitivanje osetljivosti na antimikrobne lekove je sprovedeno E-testom na odgovarajućoj hranljivoj podlozi. Tumačenje rezultata ispitivanja osetljivosti na antimikrobne lekove usklađeno je sa standardima EUCAST, prema kojima je izolat NG osetljiv na ciprofloksacin ako je minimalna inhibitorna koncentracija (MIK) manja ili jednaka 0,03 mg/l, a rezistentan ako je MIK veća od 0,06 mg/l. U statističkoj analizi podataka korišćen je χ^2 test.
Rezultati: Rezistencija gonokoka na ciprofloksacin registrovana je kod 67,3% pacijenata. Muškarci oboleli od gonoreje kod kojih je utvrđena rezistencija NG na ciprofloksacin značajno češće su pripadali grupi muškaraca koji imaju seksualne odnose sa muškarcima (MSM) ($p = 0,004$) i češće su imali podatak o prethodnom obolevanju od gonoreje u ličnoj anamnezi ($p < 0,05$).
Zaključak: Visoka prevalencija izolata NG rezistentnih na ciprofloksacin, naročito među pripadnicima MSM populacije, ukazuje na potrebu za izbegavanjem empirijske primene ovog leka u lečenju gonoreje u ovoj populaciji, kao i neophodnost ispitivanja osetljivosti izolata gonokoka na antimikrobne lekove.

Ključne reči: *Neisseria gonorrhoeae*, ciprofloksacin, antimikrobna rezistencija, MSM

Uvod

Gonoreja je akutna polno prenosiva infekcija koju izaziva *Neisseria gonorrhoeae* i koja zahvata cilindrični i prelazni epitel uretre, cerviksa, rektuma i farinksa. Izuzev gonoroičnog uretritisa, kod kojeg su simptomi oboljenja manifestni, infekcije na ostalim lokalizacijama obično su asimptomatske, zbog čega se inficirane osobe često ne leče i ostaju kontagiozne, a mogu nastati komplikacije, naročito kod žena, u vidu zapaljenske bolesti male karlice i infertiliteta.

Procene Svetske zdravstvene organizacije pokazuju da se globalno na godišnjem nivou gonorejom inficira oko 87 miliona osoba (1). Prema podacima Evropskog centra za prevenciju i kontrolu bolesti (ECDC – *European Centre for Disease Prevention and Control*), tokom 2022. godine u 28 zemalja Evropske unije (EU) potvrđen je 70.881 slučaj gonoreje (17,9/100.000), što predstavlja povećanje od 59% u odnosu na 2018. godinu (2). Najveći broj slučajeva gonoreje u zemljama EU u 2022. godini registrovan je u populaciji muškaraca koji imaju seksualne odnose sa muškarcima (MSM) (60%), a potom kod osoba oba pola uzrasta od 20 do 24 godine.

Podaci iz Gradskog zavoda za javno zdravlje u Beogradu (3) pokazuju da je u poslednjem petogodišnjem periodu došlo do porasta incidencije

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CIPROFLOXACIN-RESISTANT *NEISSERIA GONORRHOEAE* IN MEN TREATED FOR GONOCOCCAL URETHRITIS AT THE CITY INSTITUTE FOR SKIN AND VENEREAL DISEASES IN BELGRADE

Milan Bjekić[1], Tatjana Bojović Aleksić[2], Maja Vivoda[2]
[1]City Institute for Skin and Venereal Diseases, Belgrade, Serbia
[2]Institute of Public Health of Serbia "Dr. Milan Jovanović Batut", Belgrade, Serbia
Corresponding author: Milan Bjekić, City Institute for Skin and Venereal Diseases, Džordža Vašingtona 17, 11000 Belgrade, Serbia; e-mail: milinkovski@gmail.com

SUMMARY

Background/Aim: Gonorrhea is an acute sexually transmitted infection caused by *Neisseria gonorrhoeae* (NG), which affects the columnar and transitional epithelium of the urethra, cervix, rectum, and pharynx. Over the past decade, an increase in NG resistance to antibiotics from the macrolide, tetracycline, and quinolone groups has been reported in European Union countries, while resistance to ceftriaxone has remained extremely rare. The aim of this study was to determine the frequency of ciprofloxacin-resistant NG strains among patients treated for gonococcal urethritis, as well as the characteristics of patients with gonorrhea in relation to antimicrobial resistance.
Methods: The study included 55 men who presented to a dermatologist due to purulent urethral discharge. Data on patient age, sexual orientation, previous history of gonorrhea, and HIV status were obtained from the medical records of patients diagnosed with gonorrhea. Clinical samples for NG culture were collected using appropriate swabs, inoculated onto selective and non-selective culture media, and incubated in a humid atmosphere containing 5% CO_2 at 37°C for 18–24 hours. Oxidase-positive colonies were analyzed using the MALDI-TOF MS (matrix-assisted laser desorption ionization time-of-flight) system, which confirmed the identification of NG. Antimicrobial susceptibility testing was performed using the E-test method on appropriate culture media. Interpretation of antimicrobial susceptibility results was performed in accordance with the standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), according to which an NG isolate is considered sensitive to ciprofloxacin if the minimum inhibitory concentration (MIC) is less than or equal to 0.03 mg/L, and resistant if the MIC is greater than 0.06 mg/L. Statistical data analysis was performed using the χ^2 test.
Results: Ciprofloxacin resistance was detected in 67.3% of patients. Men with gonorrhea who had ciprofloxacin-resistant NG isolates were significantly more likely to be men who have sex with men (MSM) ($p = 0.004$) and to have a previous history of gonorrhea in their personal medical history ($p < 0.05$).
Conclusion: The high prevalence of ciprofloxacin-resistant NG isolates, particularly among the MSM population, indicates the need to avoid the empirical use of this drug for the treatment of gonorrhea in this population, as well as the need for antimicrobial susceptibility testing of gonococcal isolates.

Keywords: *Neisseria gonorrhoeae*, ciprofloxacin, antimicrobial resistance, MSM

Introduction

Gonorrhea is an acute sexually transmitted infection caused by *Neisseria gonorrhoeae*, which affects the columnar and transitional epithelium of the urethra, cervix, rectum, and pharynx. Except for gonococcal urethritis, which is symptomatic, infections in other localizations are usually asymptomatic, and therefore, infected persons are not treated, they are contagious, and complications may arise, especially in women in the form of pelvic inflammatory disease and infertility.

The World Health Organization estimates that 87 million new cases of gonorrhea occur globally each year (1). According to the data of the European Centre for Disease Prevention and Control (ECDC) for 2022, 70,881 confirmed cases of gonorrhea (17.9/100,000) were reported in 28 European Union countries, which is a 59% increase compared to 2018 (2). The highest infection rates in EU countries in 2022 were reported in the population of men who have sex with men – MSM (60%), and then among both men and women in the age group 20 to 24 years.

Data from the City Institute of Public Health in Belgrade (3) show that the incidence of gonorrhea has increased by 90.9% in the last five-year period (from 5.48/100,000 in 2021 to 10.46/100,000

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gonoreje za 90,9% (sa 5,48/100.000 stanovnika u 2021. godini na 10,46/100.000 stanovnika u 2025. godini). Uvođenje savremenih dijagnostičkih metoda za gonoreju, uključujući molekularnu dijagnostiku zasnovanu na amplifikaciji nukleinskih kiselina (engl. *Nucleic Acid Amplification Tests* – NAATs), kao i uzorkovanje sa ekstragenitalnih lokacija (farinks i/ili rektum), dovelo je do otkrivanja i lečenja većeg broja asimptomatskih nosilaca infekcije u našoj sredini (4).

U poslednjoj deceniji u zemljama EU došlo je do porasta rezistencije *Neisseria gonorrhoeae* na antibiotike iz grupe makrolida, tetraciklina i hinolona, dok je rezistencija na ceftriakson bila retka i kretala se u rasponu od 0,1 do 0,2% (5).

Godine 1993. ciprofloksacin je, pored ceftriaksona i cefiksima bio preporučen kao terapijska opcija prve linije za lečenje gonoreje (6). Međutim, već krajem devedesetih godina i početkom novog milenijuma beleži se porast rezistencije na ciprofloksacin, najpre u zemljama Istočne Azije, a potom na Havajima, Pacifiku i u Kaliforniji (7). Do 2004. godine zabeleženo je značajno povećanje broja izolata gonokoka rezistentnih na ciprofloksacin kod MSM osoba, zbog čega je njegova primena u lečenju gonoreje kod pripadnika ove populacije obustavljena (8). Porast rezistencije i među heteroseksualnim osobama doveo je do isključivanja fluorohinolona iz terapijskih vodiča za empirijsko lečenje gonoreje (9). Prema preporukama ECDC, primena ciprofloksacina u dozi od 500 mg per os u jednoj dozi savetuje se samo kao alternativna terapija gonoreje kod osoba sa podatkom o teškoj formi preosetljivosti (anafilaksiji) na cefalosporine i/ili peniciline u ličnoj anamnezi ili kod osoba koje odbijaju parenteralnu terapiju (10),

Cilj ovog rada bio je da se utvrde učestalost sojeva *Neisseria gonorrhoeae* rezistentnih na ciprofloksacin kod pacijenata lečenih zbog gonoroičnog uretritisa u Gradskom zavodu za kožne i venerične bolesti u Beogradu i karakteristike obolelih od gonoreje u odnosu na antimikrobnu rezistenciju.

Metode

U istraživanje je uključeno 55 muškaraca koji su se, u periodu od 1. oktobra 2024. godine do 31. decembra 2025. godine, javili na pregled u Gradski zavod za kožne i venerične bolesti u Beogradu zbog gnojnog iscetka iz uretre. Podaci o uzrastu pacijenata, seksualnoj orijentaciji, prethodnom obolevanju od gonoreje i HIV statusu preuzeti su iz internih prijava za notifikaciju kontakata obolelih od gonoreje. Dijagnoza gonoroičnog uretritisa postavljena je uzorkovanjem uretralnog sekreta bojenog po Gramu i potvrdom prisustva brojnih polimorfonuklearnih leukocita sa intracelularnim i ekstracelularnim Gram-negativnim diplokokama u direktnom mikroskopskom preparatu. Klinički uzorci pacijenata za kultivaciju *Neisseria gonorrhoeae* prikupljeni su odgovarajućim brisevima sa aluminijumskom drškom i vrhom od viskoze. Brisevi sadrže Amiesov transportni gel sa aktivnim ugljem, koji omogućava kultivaciju aerobnih, anaerobnih i zahtevnih bakterija, kao i neutralizaciju bakterijskih toksina (11). Nakon uzorkovanja, brisevi su obrađivani u laboratoriji Odseka za urogenitalne infekcije Instituta za javno zdravlje Srbije radi identifikacije uzročnika i ispitivanja osetljivosti na antimikrobne lekove. Uzorci su zasejani na neselektivnu i selektivnu hranljivu podlogu (*Modified Thayer - Martin* - MTM) i inkubiran u vlažnoj sredini sa 5% CO_2 na 37^oC tokom 18-24 h. Oksidaza-pozitivne kolonije su ispitivane MALDI-TOF MS (*Matrix-Assisted Laser Desorption Ionization Time-of-Flight*) sistemom, čime je potvrđena identifikacija *Neisseria gonorrhoeae* (12). Ispitivanje osetljivosti na antimikrobne lekove sprovedeno je E-testom (*MIC gradient stripe test method*) na odgovarajućoj hranljivoj podlozi (čokoladni agar sa dodatkom suplementa za poboljšanje rasta). Najniža koncentracija antibiotika koja inhibira rast bakterije predstavlja minimalnu inhibitornu koncentraciju – MIK (13). Tumačenje rezultata ispitivanja osetljivosti na antimikrobne lekove usklađeno je sa standardima Evropskog komiteta za ispitivanje osetljivosti na antimikrobne lekove (EUCAST – *European Committee on Antimicrobial Susceptibility Testing*), prema kojima je izolat *Neisseria gonorrhoeae* osetljiv na ciprofloksacin ako je MIK manji ili jednak 0,03 mg/l, a rezistentan ako je MIK veći od 0,06 mg/l (12). U statističkoj analizi podataka o karakteristikama muškaraca sa gonoroičnim uretritisom u odnosu na rezistenciju *Neisseria gonorrhoeae* na ciprofloksacin korišćen je χ^2 test.

Rezultati

U Tabeli 1 prikazane su karakteristike muškaraca sa gonoroičnim uretritisom u odnosu na rezistenciju *Neisseria gonorrhoeae* na ciprofloksacin. Rezistencija gonokoka na ciprofloksacin registrovana je kod 67,3 % pacijenata. Muškarci oboleli od gonoreje kod kojih je utvrđena rezistencija *Neis-*

in 2025). The introduction of modern diagnostics of gonorrhea in the form of molecular diagnostics based on the amplification of genetic material (nucleic acid amplification tests – NAATs) as well as sampling from extragenital locations (pharynx and/or rectum) led to the detection and treatment of a large number of asymptomatic carriers of the infection in our environment (4).

In the last decade, countries of the European Union have reported an increase in *Neisseria gonorrhoeae* resistance to antibiotics from the macrolide, tetracycline and quinolone groups, while resistance to ceftriaxone has remained extremely rare, and ranged from 0.1 to 0.2% (5).

In 1993, ciprofloxacin, along with ceftriaxone and cefixime, was recommended as the first line therapy for gonorrhea (6), but at the end of 1990s and the beginning of the new millennium, an increase of resistance to ciprofloxacin was reported, first in the countries of East Asia, then in Hawaii, the Pacific and in California (7). By 2004, a significant increase in the number of gonococcal isolates resistant to ciprofloxacin had been recorded in MSM, leading to the discontinuation of the drug in this population (8), while the increase in resistance among heterosexuals also led to the exclusion of fluoroquinolones from therapeutic guidelines for the empiric treatment of gonorrhea (9). According to the ECDC recommendations, the use of a single 500 mg dose of ciprofloxacin perorally is advised only as an alternative treatment of gonorrhea in persons who have data on the severe form of hypersensitivity (anaphylaxis) to cephalosporins and/or penicillin in their personal history, or who refuse to receive parenteral therapy (10).

The aim of this study was to determine the frequency of ciprofloxacin-resistant *Neisseria gonorrhoeae* strains in patients treated for gonococcal urethritis at the City Institute for Skin and Venereal Diseases in Belgrade, as well as the characteristics of gonorrhea patients in relation to antimicrobial resistance.

Methods

The study included 55 men who presented to a dermatologist at the City Institute for Skin and Venereal Diseases in Belgrade from October 1st, 2024 to December 31st, 2025 due to purulent urethral discharge. Data on patients' age, sexual orientation, previous history of gonorrhea, and HIV status were obtained from the internal records for partner notification of gonorrhea patients. The diagnosis of gonococcal urethritis was established by sampling the Gram-stained smear of urethral discharge and confirming the presence of numerous polymorphonuclear leukocytes with intracellular and extracellular Gram-negative diplococci in the direct microscopic preparation. Clinical samples for *Neisseria gonorrhoeae* culture were collected using appropriate swabs with an aluminum handle and a viscose tip. The swab also contains Amies transport gel with activated carbon, which is suitable for the cultivation of aerobic, anaerobic and fastidious bacteria, as well as the neutralization of bacterial toxins (11). After sampling, the swabs were analyzed in the laboratory of the Department of Urogenital Infections of the Institute of Public Health of Serbia, to identify the causative agent and test sensitivity to antimicrobial drugs. The swabs were inoculated onto selective and non-selective culture media (Modified Thayer-Martin-MTM) and incubated in a humid atmosphere containing 5% CO_2 at 37^{0}C for 18-24 hours. Oxidase-positive colonies were analyzed using the MALDI-TOF-MS (Matrix-Assisted Laser Desorption Ionization Time-of-Flight) system, which confirmed NG identification (12). Antimicrobial susceptibility testing was performed using the E-test method (MIC gradient stripe test method) on appropriate culture media (chocolate agar base with the addition of supplements that enhance growth). The lowest concentration of antibiotics that inhibits the growth of bacteria represents the minimum inhibitory concentration – MIC (13). The interpretation of antimicrobial susceptibility results was aligned with the standards prescribed by EUCAST (European Committee on Antimicrobial Susceptibility Testing), according to which an NG isolate is considered sensitive to ciprofloxacin if the minimum inhibitory concentration (MIC) is less than or equal to 0.03 mg/L, and resistant if the MIC is greater than 0.06 mg/L (12). The χ^2 test was used in the statistical analysis of data on the characteristics of men with gonococcal urethritis in relation to men with antimicrobial resistance of *Neisseria gonorrhoeae* to ciprofloxacin.

Results

Some characteristics of men with gonococcal urethritis in relation to the antimicrobial resistance of *Neisseria gonorrhoeae* to ciprofloxacin were shown in Table 1. Resistance of gonococci to ciprofloxacin was recorded in 67.3% of patients. Men di-

seria gonorrhoeae na ciprofloksacin su značajno češće bili homoseksualne orijentacije (p = 0,004) i imali su podatak o prethodnom obolevanju od gonoreje u ličnoj anamnezi (p < 0,05). Nije utvrđena značajna razlika u uzrastu između ispitanika, pri čemu je skoro 90% njih bilo uzrasta 25 i više godina. Veći procenat HIV-pozitivnih osoba registrovan je u grupi muškaraca kod kojih je utvrđena rezistencija gonokoka na ciprofloksacin (18,9% *vs*. 11,1%) ali ta razlika nije bila statistički značajna.

Tabela 1. Karakteristike muškaraca sa gonoroičnim uretritisom u odnosu na rezistenciju *Neisseria gonorrhoeae* na ciprofloksacin

Karakteristike	Ciprofloksacin rezistentna *Neisseria gonorrhoeae* n=37 (67,3%)	Ciprofloksacin osetljiva *Neisseria gonorrhoeae* n=18 (32,7%)	Ukupno n=55 (100%)	p*
Uzrast:				
≤ 24 godine	4 (10,8)	2 (11,1)	6 (10,9)	
≥ 25 godina	33 (89,2)	16 (88,9)	49 (89,1)	0,974
MSM status:				
Ne	4 (10,8)	8 (44,4)	12 (21,8)	
Da	33 (89,2)	10 (55,6)	43 (78,2)	0,004
Gonoreja u ličnoj anamnezi:	21 (56,8)	5 (27,8)	26 (47,3)	0,043
HIV status:				
Negativan	30 (81,1)	16 (88,9)	46 (83,6)	
Pozitivan	7 (18,9)	2 (11,1)	9 (16,4)	0,462

MSM – muškarci koji imaju seksualne odnose sa muškarcima, *p vrednost prema rezultatima χ^2 testa

Diskusija

Prema rezultatima našeg istraživanja, prevalencija ciprofloksacin-rezistentnih izolata *Neisseria gonorrhoeae* iznosila je 67,3% i češće je registrovana među MSM osobama, kao i kod ispitanika koji su prethodno obolevali od gonoreje.

Studija sprovedena početkom ovog veka u Sjedinjenim Američkim Državama (SAD), koja je analizirala razlike u antimikrobnoj rezistenciji *Neisseria gonorrhoeae* između MSM osoba i heteroseksualnih osoba, pokazala je da su izolati poreklom od MSM osoba imali značajno veću prevalenciju rezistencije na ciprofloksacin, peniciline i tetracikline (14). Prevalencija hinolon-rezistentnih sojeva *Neisseria gonorrhoeae* u SAD rasla je brže u MSM populaciji nego među heteroseksualnim osobama. Naime, u periodu od 2002. do 2003. godine prevalencija hinolon-rezistentnih sojeva gonokoka kod MSM osoba porasla je sa 1,8% na 4,9%, dok je kod heteroseksualnih osoba zabeležen minimalan porast, sa 0,2% na 0,4% (15). Studija iz Australije pokazala je da je prevalencija izolata *Neisseria gonorrhoeae* rezistentnih na ciprofloksacin porasla sa 3% u 1998. godini na 11% u 2001. godini (16).

Istraživanje sprovedeno u Španiji, koje je ispitivalo antimikrobnu rezistenciju gonokoka među heteroseksualnim osobama i MSM populacijom, pokazalo je da je rezistencija *Neisseria gonorrhoeae* na antibiotike bila značajno veća kod heteroseksualnih osoba, pri čemu su statistički značajne razlike utvrđene u rezistenciji na cefiksim i ciprofloksacin (17). Istraživanje je takođe pokazalo cirkulaciju različitih gonokoknih sojeva među ispitanicima. Naime, MSM osobe bile su sklonije infekciji sojevima genogrupa G2992 i G2400 u poređenju sa heteroseksualnim osobama, koji su češće bile inficirane

agnosed with gonorrhea in whom the antimicrobial resistance of *Neisseria gonorrhoeae* to ciprofloxacin was identified were significantly more likely to be homosexual (p=0.004) and to have a previous history of gonorrhea in their personal medical history (p<0.05). There were no significant differences between respondents in relation to age, namely, almost 90% of them were aged 25 and older. A higher percentage of HIV-positive persons was registered in the group of men where resistance of gonococci to ciprofloxacin was recorded (18.9 vs. 11.1), but his difference was not statistically significant.

Table 1. Characteristics of men with gonococcal urethritis in relation to *Neisseria gonorrhoeae* resistance to ciprofloxacin

Characteristics	Ciprofloxacin-resistant *Neisseria gonorrhoeae* n=37 (67.3%)	Ciprofloxacin-susceptible *Neisseria gonorrhoeae* n=18 (32.7%)	Total n=55 (100%)	p*
Age:				
≤ 24 years	4 (10.8)	2 (11.1)	6 (10.9)	
≥ 25 years	33 (89.2)	16 (88.9)	49 (89.1)	0.974
MSM status:				
No	4 (10.8)	8 (44.4)	12 (21.8)	
Yes	33 (89.2)	10 (55.6)	43 (78.2)	0.004
Previous history of gonorrhoea:	21 (56.8)	5 (27.8)	26 (47.3)	0.043
HIV status:				
Negative	30 (81.1)	16 (88.9)	46 (83.6)	
Positive	7 (18.9)	2 (11.1)	9 (16.4)	0.462

MSM – men who have sex with men, *p value according to the χ^2 test

Discussion

According to the results of our study, the prevalence of ciprofloxacin-resistant *Neisseria gonorrhoeae* amounted to 67.3% and it was more frequently registered in the isolates of MSM, as well as in respondents who had a previous history of gonorrhea.

A study from the beginning of this century conducted in the United States of America that analyzed differences in antimicrobial resistance of *Neisseria gonorrhoeae* among MSM and heterosexuals showed that isolates in MSM had a significantly higher prevalence of resistance to ciprofloxacin, penicillin and tetracyclines (14). The prevalence of quinolone-resistant strains of *Neisseria gonorrhoeae* in the USA increased more rapidly in the MSM population compared to heterosexual individuals. Namely, in the period from 2002 to 2003, the prevalence of quinolone-resistant strains of gonococci in MSM increased from 1.8% to 4.9%, while a minimal increase from 0.2% to 0.4% was recorded in heterosexuals (15). A study from Australia showed that isolates of *Neisseria gonorrhoeae* resistant to ciprofloxacin increased from 3% in 1998 to 11% in 2001 (16).

A study conducted in Spain that examined the antimicrobial resistance of gonococci among heterosexuals and MSM showed that the resistance of *Neisseria gonorrhoeae* to antibiotics was significantly higher in heterosexuals, while differences in the resistance to cefixime and ciprofloxacin were statistically significant (17). The study also showed the circulation of different gonococcal strains among the respondents, namely MSM were more prone to infection with strains belonging to genogroups G2992 and G2400 compared to heterosexuals who were more often infected with strains belonging to genogroup G1407 which is the most prevalent in Eu-

sojevima genogrupe G1407, koja je ujedno i najzastupljenija u Evropi. U pomenutoj studiji, četvrtina ispitanika imala je neku polno prenosivu infekciju tokom prethodne godine, pri čemu je najčešća bila gonoreja, registrovana kod 12,1% osoba. U našem istraživanju nismo ispitivali podatak o obolevanju od gonoreje tokom prethodne godine, ali je 47,3% naših ispitanika prethodno imalo ovu infekciju, dok je 16,4% bilo HIV-pozitivno. Studija sprovedena na Kipru među osobama koje žive sa HIV-om pokazala je značajnu povezanost podataka o polno prenosivim infekcijama u ličnoj anamnezi sa pojavom antimikrobne rezistencije (18).

Rezultati našeg istraživanja o prevalenciji rezistencije gonokoka na ciprofloksacin (67,3%) u skladu su sa rezultatima drugih autora. Prema podacima ECDC za 2022. godinu, prevalencija gonokoka rezistentnih na ciprofloksacin u zemljama EU iznosila je 65,9% (19). Studija iz Katalonije pokazala je da se prevalencija rezistencija *Neisseria gonorrhoeae* na ciprofloksacin povećala za 16,5%, sa 61,7% u 2019. godini na 71,9% u periodu 2022-2023. godine (20).

Hinoloni deluju inhibicijom DNK-giraze i topoizomeraze IV, što rezultira baktericidnim dejstvom leka (21). Bakterije razvijaju rezistenciju na hinolone kroz mutacije koje menjaju mesto vezivanja hinolona za ove ciljne enzime. DNK-giraza sastoji se od dve GyrA i dve GyrB podjedinice. Kod gonokoka, početne mutacije u primarnom ciljnom genu, gyrA, povezane su sa rezistencijom. Mutacije u genu gyrA smanjuju afinitet vezivanja hinolona, čineći enzim DNK-girazu otpornom na njegov inhibitorni efekat. Topoizomeraza IV je tetramer koji se sastoji od dve ParC i dve ParE podjedinice. Enzimska aktivnost topoizomeraze IV takođe može biti inhibirana hinolonima, iako su za njenu inhibiciju *in vitro* potrebne veće koncentracije nego za inhibiciju DNK giraze. Specifični jednonukleotidni polimorfizam (engl. *Singl-Nucleotide Polymorphism* – SNP), odnosno promena jednog nukleotida u genu gyrA, sam po sebi dovodi do rezistencije niskog do srednjeg nivoa, dok rezistencija visokog nivoa zahteva jednu ili nekoliko specifičnih pratećih mutacija u parC. Ove mutacije mogu nastati izlaganjem subinhibitornim koncentracijama ciprofloksacina, naročito u MSM populaciji, za koju je karakteristično češće testiranje na polno prenosive bolesti, što ima za posledicu češću upotrebu antibiotika (21). *Neisseria gonorrhoeae* može horizontalnim transferom gena preuzeti gene povezane sa rezistencijom od drugih vrsta roda *Neisseria* koje pripadaju fiziološkom mikrobiomu, što predstavlja jedan od mogućih puteva nastanka antimikrobne rezistencije (22).

Prema rezultatima našeg istraživanja, skoro 90% ispitanika bilo je uzrasta 25 i više godina. Prema podacima Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut" (23), u 2023. godini najviše uzrasno-specifične stope obolelih od gonoreje zabeležene su u uzrasnoj grupi od 20 do 29 godina (6,60/100.000), a potom u grupi 30 do 39 godina (5,01/100.000). Studija iz Katalonije pokazala je da je uzrast ≥ 25 godina povezan sa većom učestalošću rezistencije gonokoka na ciprofloksacin, tetracikline i peniciline (20).

Glavno ograničenje ovog istraživanja jeste to što su ispitivanu populaciju činili isključivo pacijenti koji su se javili u Gradski zavod za kožne i venerične bolesti u Beogradu, zdravstvenu ustanovu koja pruža usluge dijagnostike i lečenja gonoreje najvećem broju pripadnika gradske populacije Beograda. Stoga je upitno u kojoj meri se dobijeni rezultati mogu odnositi na opštu populaciju.

Zaključak

Visoka prevalencija izolata *Neisseria gonorrhoeae* rezistentnih na ciprofloksacin u našoj populaciji, naročito među muškarcima koji imaju seksualne odnose sa muškarcima, ukazuje na značaj praćenja antimikrobne rezistencije gonokoka i potrebu za ispitivanjem osetljivosti izolata na antimikrobne lekove. Dobijeni rezultati ukazuju i na potrebu da se ciprofloksacin ne primenjuje empirijski u lečenju gonoreje, dok ceftriakson, u dozi od 1 g intramuskularno, ostaje lek izbora za lečenje ove polno prenosive infekcije.

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rope. In the mentioned study, ¼ of the respondents had a sexually transmitted infection in the previous year, and the most common was gonorrhea, which was registered in 12.1% of persons. In our study, we did not examine data on gonorrhea in the previous year, but 47.3% of our respondents had this infection at some point in their lives, and 16.4% of them were HIV positive. A study conducted in Cyprus among persons living with HIV showed a significant association between personal history of sexually transmitted infections and the occurrence of antimicrobial resistance (18).

The results of our study on the prevalence of gonococcal resistance to ciprofloxacin (67.3%) are consistent with the results of other authors. According to the ECDC data for 2022, the prevalence of gonococci resistant to ciprofloxacin in EU countries was 65.9% (19). It was reported in the study from Catalonia that resistance of *Neisseria gonorrhoeae* to ciprofloxacin increased by 16.5%, from 61.7% in 2019 to 71.9% in the period 2022-2023 (20).

Quinolones act by inhibiting DNA gyrase and topoisomerase IV, which results in the bactericidal effect of the drug (21). Bacteria develop resistance to quinolones through mutations that alter the recognition of quinolones by these target enzymes. DNA gyrase consists of two GyrA subunits and two GyrB subunits. In gonococci, initial mutations in the primary target gene, gyrA, are associated with the resistance. Mutations in gyrA reduce the binding affinity of quinolones, making the DNA gyrase enzyme resistant to its inhibitory effect. Topoisomerase IV is a tetramer that is composed of two ParC and two ParE subunits. The enzyme activity of topoisomerase IV can also be inhibited by quinolones, although higher concentrations than those necessary for the inhibition of DNA gyrase in vitro are required. Specific single nucleotide polymorphism – SNP, that is, a single nucleotide variation in gyrA on its own provides a low to medium level resistance, but high-level resistance requires one or several specific accompanying mutations in parC. These mutations are easily caused by exposure to subinhibitory concentrations of ciprofloxacin, especially in the MSM population, which is characterized by more frequent testing for sexually transmitted infections, resulting in a more frequent use of antibiotics (21). By horizontal gene transfer, *Neisseria gonorrhoeae* can take up resistance genes from other *Neisseria* that belong to the physiological microbiome, which is a common route of occurrence of antibiotic resistance (22).

According to the results of our study, almost 90% of respondents were 25 years old and older. According to the data of the Institute of Public Health of Serbia Dr "Milan Jovanovic Batut" (23) in 2023, the highest age-specific rates of gonorrhea were in the age group 20 to 29 years (6.60/100,000) and then in the group 30 to 39 years (5.01/100,000). A study from Catalonia described that age ≥ 25 years was associated with the higher resistance of gonococci to ciprofloxacin, tetracyclines and penicillin (20).

The main limitation of this study is that the examined population consisted exclusively of patients who came to the City Institute for Skin and Venereal Diseases in Belgrade, which represents a health institution where the largest number of members of the city population of Belgrade are treated for gonorrhea, and therefore, it is questionable whether the obtained results can be applied to the general population.

Conclusion

The high prevalence of ciprofloxacin-resistant *Neisseria gonorrhoeae* isolates in our population, particularly in men who have sex with men who are diagnosed with gonorrhea most frequently, indicates the need to discontinue the use of ciprofloxacin in the empiric treatment of gonorrhea, the importance of antimicrobial susceptibility testing and that one gram of ceftriaxone intramuscularly remains the first-line drug in the treatment of this sexually transmitted infection.

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