

Upotreba antibiotika i antivirotika u lečenju pacijenata obolelih od COVID-19 u Kovid ambulanti Doma zdravlja Golubac

Boban M. Trifunović

Dom zdravlja Golubac, Golubac, Srbija

Use of antibiotics and antivirals in the treatment of COVID-19 patients in the COVID outpatient clinic of Primary Healthcare Center Golubac

Boban M. Trifunovic

Primary Healthcare Center Golubac, Golubac, Serbia

Sažetak

Uvod: U Srbiji je izdato 13 protokola o lečenju COVID-19 infekcije. U svim protokolima je naglašavan značaj nedavanja antibiotika rutinski, posebno pacijentima koji su lečeni na primarnom nivou zdravstvene zaštite. Primena antibiotika je široko rasprostranjena u lečenju obolelih od COVID-19, u celom svetu.

Cilj rada: Ispitati učestalost, vrste i kombinacije primenjenih antibiotika i antivirotika kod pacijenata obolelih od COVID-19.

Metod: Opservacijska retrospektivna studija preseka o propisivanju antibiotika i antivirotika pacijentima koji su lečeni u Kovid ambulanti Doma zdravlja Golubac u periodu od 17.7.2020. do 31.10.2022. godine. Podaci su dobijeni iz elektronskih kartona pacijenata. Uzorak je činilo 2709 ispitanika. Varijable koje smo koristili pol, godine starosti, Za obradu podataka koristili smo statistički paket SPSS17. Od statističkih metoda koristili smo deskriptivnu statistiku frekvencu (%), X2 test.

Rezultati: Istraživanjem je obuhvaćeno 2 709 pacijenata. Ukupno je bilo 1590 osoba kojima je prepisan antibiotik. U odnosu na ukupan broj obolelih, koji su pregledani u Kovid ambulanti, to predstavlja 58,7%. Najveći procenat obolelih kojima je prepisan antibiotik je u periodu novembar 2020 – maj 2021. godine. U zavisnosti od perioda ispitivanja, cefalosporini i azithromycin su najčešće prepisivani antibiotici (70–89% ukupnog broja prepisivanih antibiotika). Najčešće prepisivana kombinacija antibiotika je cefalosporin-fluorohinolon.

Zaključak: Upotreba antibiotika u lečenju obolelih od oboljenja COVID-19 je veća od preporučene protokolima i vodičima dobre kliničke prakse.

Abstract

Introduction: There were 13 protocols for the COVID-19 infection treatment in Serbia. All protocols emphasize the importance of not giving antibiotics routinely, especially in patients who were treated at the primary healthcare level. Use of antibiotics was widely spread in the treatment of COVID-19 patients, all around the world.

Objective. We aimed at examining the incidence, type, and combination of used antibiotics and antivirals in COVID-19 patients.

Method: Observational retrospective cross-sectional study on the prescription of antibiotics and antivirals in patients who were treated in the COVID clinic of the Golubac Primary Healthcare Center in the period from 7/17/2020. until 10/31/2022. The data were obtained from the electronic health records of the participants. The sample consisted of 2709 respondents. The variables we used were sex and age. We used the statistical package SPSS17 for data processing. For statistical methods, we used descriptive statistics frequency (%) and, the X2 test.

Results: The research included 2,709 patients. In total, 1590 people were prescribed antibiotics. Concerning the total number of patients, examined in the COVID clinic, this represents 58.7%. The highest percentage of patients who were prescribed an antibiotic was in the period November 2020 - May 2021. Depending on the study period, cephalosporin and azithromycin are the most frequently prescribed antibiotics (70–89% of the total number of prescribed antibiotics). The most commonly prescribed antibiotic combination is a cephalosporin-fluoroquinolone.

Conclusion. The use of antibiotics in the treatment of COVID-19 patients was higher than recommended in the protocols and guidelines.

Uvod

Korona virus pripada grupi virusa koji uzrokuju bolest u rasponu od blage prehlade do teškog akutnog respiratornog sindroma (SARS). Procenjuje se da virusi iz ove grupe prouzrokuju oko polovine svih respiratornih infekcija kod čoveka. Virus SARS-CoV-2 je prouzrokovač pandemije, koja je počela 2020. godine¹.

Dijagnoza se postavlja na osnovu anamneze, kliničke slike, fizikalnog pregleda, specifičnih virusnih testova (RT-PCR, brzi antigenski test). Većina obolelih (80,0%) je bez tegoba ili ima blagu formu bolesti koja se manifestuje simptomima respiratorne infekcije sa povišenom telesnom temperaturom. Veliki broj obolelih je imao i gastrointestinalne tegobe, gubitak ili izmenjeno čulo ukusa i/ili mirisa. Teža simptomatologija u vidu gušenja, izrazitog zamaranja i nastavka povišene telesne temperature se javlja uglavnom kod starijih bolesnika i onih sa hroničnim oboljenjima (20%). Mortalitet od ovog oboljenja je oko 3%².

U cilju efikasnog lečenja obolelih od COVID-19 infekcije, izrađeno je 13 protokola lečenja. Protokolima je predviđeno da se oboleli sa lakšom kliničkom slikom leče na primarnom nivou zdravstvene zaštite, u Kovid ambulantama. Preporučena terapija za njihovo lečenje je podrazumevala simptomatsku i vitaminsku terapiju (antipiretici, vitamin D, vitamin C), preporuku za odmorom i adekvatnim unosom tečnosti. Striktnu primenu protokola je otežavala preopterećenost zdravstvenog sistema u pojedinim periodima epidemije, tako da su mnogi pacijentima sa upalom pluća i saturacijom ispod 94%, koje bi po protokolima trebalo uputiti na bolničko lečenje, lečeni u Kovid ambulantama i kućnim uslovima.

Za lečenje obolelih od COVID-19 u Kovid ambulantama, dostupni su antivirusici od marta 2021. godine. Najpre je bio na raspolaganju antivirusik Favipiravir, od januara 2022. Molnupiravir, a od jula 2022. Ritonavir.

U svim protokolima je naglašavan značaj nedavanja antibiotika po navici, posebno pacijentima koji su zbog težine bolesti lečeni na primarnom nivou zdravstvene zaštite. Meta analize odgovarajućih studija govore da je primena antibiotika bila široko rasprostranjena u celom svetu. Preko 60% obolelih je u lečenju ovog oboljenja dobijalo antibiotike³. Postojao je trend smanjenja propisivanja antibiotika kako je pandemija napredovala. Najmanje su propisivani kod pacijenata koji nisu hospitalizovani (59,3%), potom kod onih koji su hospitalizovani sa lakšom ili srednje teškom kliničkom slikom (74,8%), a najviše kod pacijenata na intenzivnoj nezi (86,4%). Najviše su u terapiji upotrebljavani fluorohinoloni (20,0%) i makrolidi (18,9%). Značajan udeo u terapiji su imali i drugi antibiotici, pre svega β-laktamski antibiotici i cefalosporini po 15,0%³.

Neracionalna upotreba antibiotika i povećana otpornost bakterija su problem koji je postojao i pre ove epidemije. Najveći procenat antibiotika se prepisuje za lečenje respiratornih

Introduction

Coronavirus belongs to the virus strain which may cause the disease ranging from a mild cold to severe acute respiratory syndrome (SARS). It is estimated that these virus strains cause about half of the respiratory infections in humans. The SARS-CoV-2 virus caused the pandemic starting in 2020¹.

The disease is diagnosed based on the history, clinical presentation, physical examination, specific antiviral tests (RT-PCR, rapid antigen test). The majority of the diseased (80,0%) are either without symptoms or with mild symptoms, manifesting as a respiratory infection with fever. Many patients had gastrointestinal symptoms, loss or change in taste and/or smell. More severe symptoms, in the form of asphyxiation, extreme fatigue, and continuation of fever were noticed mostly in older patients and those with chronic diseases (20%). The mortality rate was around 3%².

For the sake of efficient treatment of COVID-19 patients, 13 protocols were produced. The protocols instructed that patients with mild clinical presentation should be treated at the primary healthcare level, in COVID outpatient clinics. The recommended therapy for their treatment included symptomatic and vitamin therapy (antipyretics, vitamin D, vitamin C), rest, and adequate fluid intake. The strict implementation of the protocol was hindered by the overburden of the health system during some periods of the outbreak. Therefore, many patients with pneumonia and saturation below 94%, who according to protocols should have been hospitalized, were treated in COVID outpatient clinics and at their homes.

For the treatment of COVID-19 patients in COVID outpatient clinics, antivirals became available in 2021. At first, Favipiravir was at our disposal from January 2022, Molnupiravir, and from July 2022, Ritonavir.

All the protocols stressed the importance of avoiding antibiotics, merely by habit, especially in patients who due to the severity of the disease were treated at the primary healthcare level. Meta-analyses of the appropriate studies confirmed that antibiotic use was widespread all around the world. Over 60% of patients were given antibiotics during COVID-19 treatment³. There was a trend toward a decrease in antibiotic prescription as the pandemic progressed. They were the least prescribed in non-hospitalized patients (59,3%), followed by those hospitalized but with mild or medium-severe clinical presentation (74,8%), and the most in the intensive care units (86,4%). The most used antibiotics were fluoroquinolones (20,0%) and macrolides (18,9%). A significant share of the COVID treatment had other antibiotics, as well, firstly β-lactams and cephalosporines, each 15,0%³.

Irrational use of antibiotics and increased bacterial resistance are the problems that existed even before the pandemic. The highest percentage of antibiotics is prescribed for the treatment of respiratory infections. Irrational use of antibiotics for acute respiratory infections contributes to bacterial

oboljenja. Neracionalna primena antibiotika za akutne infekcije respiratornog trakta doprinosi nastanku otpornosti bakterija⁴. U toku je globalna borba protiv prekomerne upotrebe antibiotika i posledične otpornosti.

Zadovoljavajuće poznavanje osobina antibiotika i najčešćih prouzrokovaca oboljenja je osnova u borbi protiv otpornosti. Racionalna primena antibiotika podrazumeva prepisivanje antibiotika u skladu sa kliničkim nalazom, ako je moguće i mikrobiološkim nalazom. Potrebno je primeniti pravi antibiotik u najpovoljnijoj dozi izborom najboljeg načina primene i trajanja lečenja.

Cilj rada

Ispitati učestalost, vrste i kombinacije primenjenih antibiotika i antivirusika kod pacijenata obolelih od COVID-19, lečenih u Kovid ambulanti Doma zdravlja Golubac.

Metod

Opservacijska retrospektivna studija preseka o propisivanju antibiotika i antivirusika pacijenata, koji su lečeni u Kovid ambulanti Doma zdravlja Golubac u periodu od 17.7.2020. do 31.10.2022. godine. Podaci su dobijeni iz elektronskih kartona pacijenata. Uzorak je činilo 2709 ispitanika. Varijable koje smo koristili pol, godine starosti, pratili propisivanje antibiotika u različitim periodima. Procenjivali smo razliku propisivanja antibiotika, godine starosti u posmatranom periodu. Za obradu podataka koristili smo statistički paket SPSS17. Od statističkih metoda koristili smo deskriptivnu statistiku frekvencu (%), X2 test.

Rezultati

Istraživanjem je obuhvaćeno 2 709 pacijenata koji su od 1.7.2020. do 31.10.2022. godine lečeni u Kovid ambulanti Doma zdravlja Golubac. Ukupno je pregledano 1 299 osoba muškog pola i 1 410 ženskog pola. Posmatrani period podeljen je u tri vremenska razmaka. Periodi su formirani na osnovu nekih zajedničkih karakteristika epidemije u tom periodu brzine prenošenja, težine kliničke slike i toka bolesti, vakcinacije, primene antivirusika. Prvi period čini vremenski razmak od jula 2020. godine do maja 2021. godine. Drugi period obuhvata vremenski razmak od jula 2021. godine do maja 2022. godine. Treći period je vremenski razmak od juna 2022. godine do kraja oktobra 2022. godine.

resistance⁴. At the moment, there is a global fight against the overuse of antibiotics and consequential resistance.

An adequate knowledge of antibiotic characteristics and the most common causes are the basis of the fight against resistance. The rational use of antibiotics includes antibiotic prescription according to clinical findings, and if possible microbiology findings. It is necessary to apply the proper antibiotic, in the most favorable dose, choosing the best way of application, and treatment duration.

Objective

We aimed at examining the incidence, type, and combination of used antibiotics and antivirals in COVID-19 patients, treated in the COVID outpatient clinic of the Primary healthcare Center Golubac.

Method

Observational retrospective cross-sectional study on the prescription of antibiotics and antivirals in patients who were treated in the COVID clinic of the Golubac Primary Healthcare Center in the period from 7/17/2020. until 10/31/2022. The data were obtained from the electronic health records of the participants. The sample consisted of 2709 respondents. The variables we used were sex and age, and we followed the prescription of antibiotics in different periods. We evaluated the difference in prescribing antibiotics and the patient's age in the observed period. We used the statistical package SPSS17 for data processing. For statistical methods, we used descriptive statistics frequency (%) and, the X2 test.

Results

The study included 2.709 patients who visited the COVID outpatient clinic of the Primary Healthcare Golubac from July 1st, 2020 until October 31st, 2022. The total number of examined male patients was 1.299 and 1.410 female patients. The reviewed period was divided into three time periods. The periods were formed based on some mutual outbreak characteristics, at the time: the speed of the disease spreading, the severity of clinical presentation and disease course, vaccination, use of antivirals. The first period was from July 2020 to May 2021. The second period was from July 2021 to May 2022. The third period was from June 2022 until the end of October 2022.

Tabela 1. Struktura uzorka po polu i starosti i broj pacijenata kojima je prepisan antibiotik po polu i uzrastu u različitim periodima
Table 1. Structure of the sample by gender and age and the number of patients who were prescribed antibiotics by gender and age in different periods

	Prvi period/ First period				Drugi period/ Second period				Treći period/ Third period				Ukupno/ Total	
	M/M		Ž/F		M/M		Ž/F		M/M		Ž/F			
	ob.	ant.	ob.	ant.	ob.	ant.	ob.	ant.	ob.	ant.	ob.	ant.	ob.	ant.
do 44 god. from 44 y	108	83	98	88	314	97	296	96	81	28	99	60	1006	452
%		76,8		89,8		30,9		32,4		34,6		60,6		44,9
45–64 god. 45–64 y	121	105	118	104	211	98	261	121	64	56	80	65	855	549
%		86,8		88,1		46,4		46,3		87,5		81,2		64,2
od 65 god from 65 y	92	87	111	76	218	117	229	130	90	82	118	97	848	589
%		94,6		68,5		53,7		56,8		91,1		82,2		69,4
ukupno Total	321	275	327	268	743	312	786	347	235	166	297	222	2709	1590
%		85,7		82,0		42,0		44,1		70,6		74,7		58,7

M - muškarci, Ž - žene; ob - oboleli od COVID-19, ant - broj obolelih kojima je prepisan antibiotik; % - procenat pacijenata kojima je prepisan antibiotik u odnosu na ukupan broj obolelih u tom periodu za taj uzrast.

Izvor: Autor

M - male, F - female; su - suffering from COVID-19, ant - the number of patients who were prescribed an antibiotic; % - the percentage of patients who were prescribed an antibiotic, compared to the total number of the diseased at the time, for the age group.

Source: Author

Ukupno je bilo 1 590 osoba kojima je prepisan antibiotik. U odnosu na ukupan broj obolelih, koji su pregledani u Kovid ambulanti, to predstavlja 58,7%. U 93% slučajeva antibiotik je prepisan na prvom lekarskom pregledu, a samo u 7% slučajeva antibiotik je prepisan na drugom lekarskom pregledu. Najveći procenat obolelih sa prepisanim antibiotikom je u prvom periodu, a najmanji u drugom periodu posmatranog perioda. U prvom periodu je bilo 648 obolelih, prepisano je 543 antibiotika (83,79%), u drugom periodu je bilo 1 529 obolela, prepisano je 659 antibiotika (43,1%), u trećem periodu je bilo 532 obolela, prepisano je 388 antibiotika (72,93%).

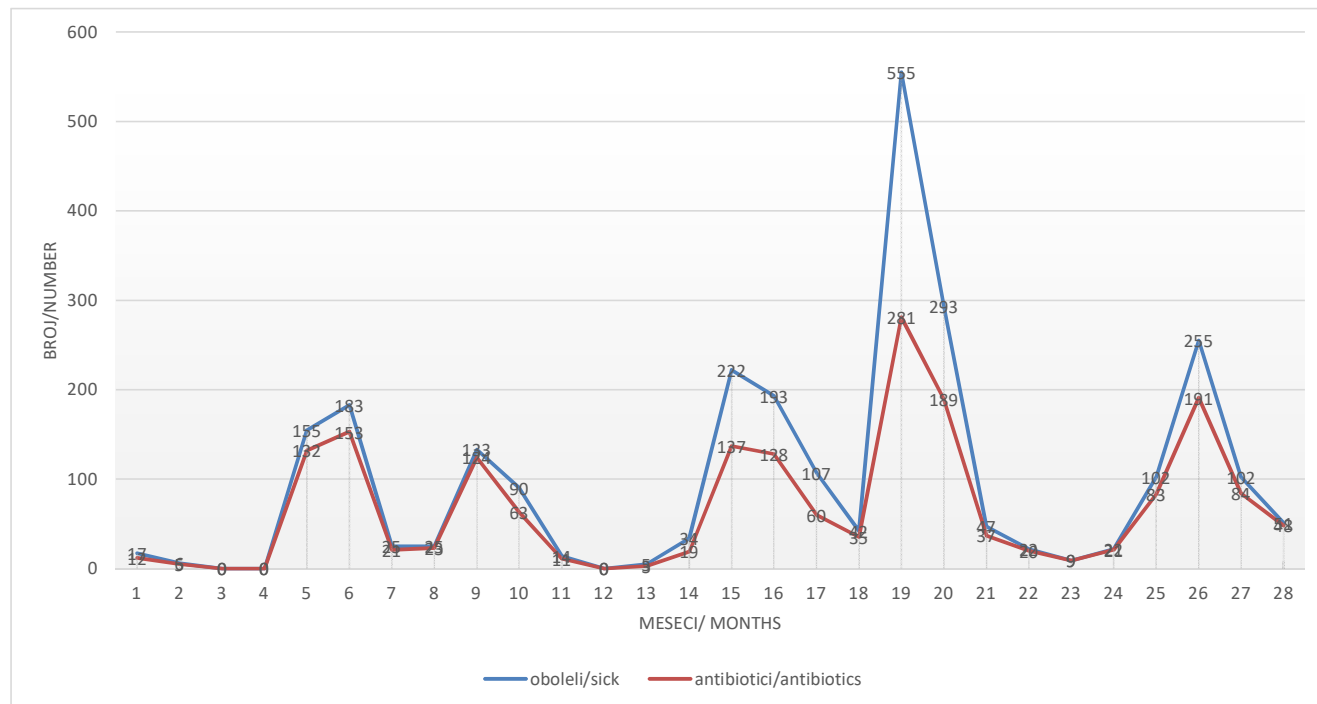
U prvom periodu nešto više antibiotika je prepisano osobama muškog pola, najviše osobama starosti 45–64 godine. U drugom i trećem periodu antibiotici su više prepisani osobama ženskog pola, najviše osobama starijim od 65 godina.

U grafikonu 1 je prikazan broj obolelih i broj osoba kojima je prepisan antibiotik po mesecima.

There were a total of 1.590 patients who were prescribed an antibiotic. Compared to the total number of examined patients in the COVID clinic it made 58,7%. In 93% of cases, the antibiotic was prescribed during the first visit and only 7% during the second visit. The highest percentage of those who were prescribed an antibiotic was in the first period and the least in the second period of the reviewed time span. In the first period, there were 648 COVID patients and 543 were prescribed an antibiotic (83,79%). In the second period, there were 1.529 COVID patients and 659 antibiotics (43,1%) were prescribed. In the third period, there were 532 COVID patients and 388 antibiotics were prescribed (72,93%).

In the first period, slightly more antibiotics were prescribed to male patients, mostly those aged 45–64. In the second and third period, antibiotics were more prescribed to female patients, mostly those over 65.

Figure 1 shows the number of COVID patients and the number of those who were prescribed an antibiotic, by month.



Grafikon 1. Broj obolelih i broj prepisanih antibiotika po mesecima
Figure 1. The number of COVID patients and prescribed antibiotics, by month

Izvor: Autor/ Source: Author

Zapaža se da je najveći procenat obolelih kojima je prepisan antibiotik u periodu novembar 2020 – maj 2021. godine. U tabeli 2 prikazana je struktura prepisanih antibiotika po posmatranim periodima.

It stands out that the highest percentage of diseased patients who were prescribed an antibiotic was from November 2020 – May 2021. Table 2 shows the structure of the prescribed antibiotics, by reviewed periods.

Tabela 2. Struktura prepisanih antibiotika u posmatranim periodima
Table 2. Structure of prescribed antibiotics in the observed periods

Antibiotik/ Antibiotic	I period	II period	III period
Cefalosporini/ Cephalosporins	44%	38%	43%
Azitromycin/ Azithromycin	29%	32%	46%
Hinoloni/ Quinolones	8%	11%	1%
Makrolidi/ Macrolides	17%	9%	4%
Penicilini/ Penicillin	2%	8%	6%
Drugi/ Others	-	2%	-

Izvor: Autor / Source: Author

Najveći broj prepisanih antibiotika činili su cefalosporini (38–44%), a potom po učešću dolazi azitromycin (29–46%), pa ostali makrolidi (4–17%), hinoloni (1–11%). Najmanje udela imao je penicilin (2–8%).

Pacijentima je najčešće prepisivan jedan antibiotik. Međutim, 137 pacijenata je dobilo dva antibiotika na jednom pregledu, što predstavlja 5% u odnosu na ukupan broj obolelih. Najviše je bilo osoba starijih od 65 godina, koje su dobile dva antibiotika - 73 (53,3% od ukupnog broja pacijenata kojima su prepisana dva antibiotika). Bilo je 50 (36,5%) pacijenata starosti 45–64 godine i 14 (10,2%) pacijenata mlađih od 45 godina kojima su prepisana dva antibiotika.

Stariji pacijenti su češće dobijali antibiotike od mlađih. Statistička značajnost razlike u učestalosti dobijanja antibiotika u odnosu na starosne grupe ispitana je χ^2 testom i prikazana u tabeli 3.

The majority of prescribed antibiotics were cephalosporins (38–44%), followed by azithromycin (29–46%), then other macrolides (4–17%), and quinolones (1–11%). The least common was penicillin (2–8%).

Patients were mostly prescribed one antibiotic. However, 137 patients got two antibiotics at a visit, which makes 5% compared to the total number of diseased. Among those who got two antibiotics, the majority were over 65 and there were 73 of them (53,3% of the total number of those who got two antibiotics). There were 50 (36,5%) patients aged 45–64 and 14 (10,2%) younger than 45 who also got two antibiotics.

Older patients got antibiotics more frequently than the younger ones. Statistical significance of the difference in the incidence of antibiotic prescription between age groups was examined using χ^2 - test and it is shown in Table 3.

Tabela 3. Statistika χ^2 testa

Table 3. Statistics of the χ^2 test

	Vrednost / Value	Značajnost / Significance
Pearson χ^2	25,399 ^a	0,000
Phi	0,126	0,000
Cramer's V	0,126	0,000

Napomena: a - 0 ćelija (0,0%) ima očekivani broj manji od 5. Minimalni očekivani broj je 36,53⁵.

Note: a - 0 cells (0.0%) have expected count less than 5. The minimum expected count is 36.53⁵.

Izvor: Autor / Source: Author

Rezultati χ^2 testa u tabeli 3 pokazuju prisustvo statistički značajne razlike u pogledu prepisanih antibiotika pacijentima različitih godina starosti (p vrednost = 0,000). To praktično znači da postoji povezanost između godina starosti i broja prepisanih antibiotika. Stariji pacijenti su statistički značajno češće dobijali dva antibiotika u odnosu na pacijente mlađe od 45 godina. Phi i Cramer's V vrednosti testa pokazuju da je ta povezanost umerena.

Ukupan broj pacijenata kojima je prepisan antivirusik iznosi 855, što je 31,76% ukupnog broja pacijenata. U odnosu na posmatrane periode, najviše antivirusika je prepisano u drugom periodu, ali je u odnosu na broj pacijenata u trećem periodu najveći procenat pregledanih kojima je prepisan antivirusik (59,80%). U tabeli 4 je izvršen prikaz prepisanih antivirusika u odnosu na ukupan broj pregleda, pol i uzrast pacijenata.

The results of the χ^2 -test, in Table 3, show a statistically significant difference concerning prescribed antibiotics to patients of different age groups (p -value = 0,000). It practically means there is a connection between age and the number of prescribed antibiotics. Older patients statistically significantly got two antibiotics more often compared to patients younger than 45. Phi and Cramer's V values tests show this connection is moderate.

The total number of patients who were prescribed antivirals was 855, which makes 31,76% of the total number of patients. Comparing reviewed periods, the highest number of antivirals were prescribed in the second period but compared to the number of patients in the third period, the highest number of examined patients were prescribed an antiviral (59,80%). In Table 4, we showed prescribed antivirals compared to the total number of visits, gender, and patient's age.

Tabela 4. Prepisani antivirusici u odnosu na ukupan broj pregleda, pol i uzrast pacijenata
Table 4. Antivirals prescribed in relation to the total number of examinations, gender and age of patients

Period	Broj pacijenata/ Number of patients	Prepisani antivirusici/ Prescribed antivirals	% prepisanih antivirusika u odnosu na ukupan broj pacijenata koji su pregledani % of prescribed antivirals compared to the total number of examined patients	Muški pol/ Male	Ženski pol/ Female	Do 45 god./ Up to 45 y	45–64 god. 45–64 y	Preko 65 god./ Over 65 y
Prvi period First period	648	1	0,15%	1	0	0	66	20
Drugi period Second period	1 529	536	35,05%	260	276	1	207	112
Treći period Third period	532	318	59,80%	138	180	0	263	186
Ukupno Total	2 709	855	100%	399	456	1	536	318

Izvor: Autor / Source: Author

Diskusija

Sprovedeno istraživanje pokazalo je da je 58,7% pacijenata prepisan antibiotik, a najviše u periodu od jula 2020. do maja 2021. godine (83,79%). Taj period karakteriše nedostatak informacija o bolesti, načinu lečenja, veliki broj pacijenata sa težom kliničkom slikom i zapaljenjem pluća, nedostatak bolničkih kapaciteta za lečenje obolelih, nije bilo antivirusika na raspolaganju u primarnoj zdravstvenoj zaštiti, najpre nepostojanje vakcina, a kasnije nedovoljan broj vakcinisanih. Osobe starije od 65 godina su u ovom periodu imale zabranu izlazaka. Često su pacijenti, koji su ispunjavali kriterijume za bolničko lečenje, lečeni u kućnim uslovima uz nadzor lekara iz Kovid ambulanti. U prvom periodu nešto više antibiotika je prepisano osobama muškog pola, najviše osobama starosti 45–64 godine. U međunarodnim studijama, koje su analizirale početak epidemije, prevalencija prepisivanja antibiotika iznosila je prosečno 74,6%, od 85,8% početkom epidemije do 62,6% u nastavku. „U Evropi je iznosila 63,1%, u Severnoj Americi je bila 64,8%, u Kini je iznosila 76,2%. Prediktori povećane upotrebe antibiotika kod COVID-19 uključuje starije godine⁴³. Prosečna stopa upotrebe antibiotika u jednoj retrospektivnoj studiji, koja je obuhvatala istraživanja iz Kine, SAD, Danske i Brazila, bila je 74,0%. Najčešće korišćeni su fluorohinoloni (56,8% pacijenata), ceftriakson (39,5% pacijenata) i azitromycin (29,1% pacijenata). Antivirusna sredstva su korišćena u 56,9% pacijenata⁶. Vremenski poklapanje sa rezultatima studije i prvim periodom ovog istraživanja ne postoji, ali je celim tokom epidemije situacija u našoj zemlji pratila situaciju u zapadnoj Evropi sa znatnim zaostatkom.

Discussion

Our research showed that 58,7% of patients were prescribed an antibiotic and the most from July 2020 until May 2021 (83,79%). This period is characterized by the lack of information about the disease, treatment options, the large number of patients with severe clinical presentation and pneumonia, the lack of hospital capacity for the treatment of the diseased, there were no antivirals at our disposal in primary health care, at first, non-existence of the vaccines, and later on not enough vaccinated people. People over 65, at this period, were forbidden to go out of their houses. Very often, patients who should have been treated at the hospital were treated at home, under the supervision of the physicians from the COVID clinics. In the first period, a bit more antibiotics were prescribed to males, mostly those aged 45–64. In the international studies that analyzed the beginning of the outbreak, the prevalence of antibiotic prescription was averaged from 74,6% to 85,8%, at the beginning, to 62,6% later on. „In Europe, it was 63,1%, in North America 64,8%, in China 76,2%. Predictors of the increased use of antibiotics in COVID-19 include older age⁴³. The average rate of antibiotic use in one retrospective study, encompassing research from China, the USA, Denmark, and Brazil was 74,0%. The most commonly used were quinolones (56,8% of patients), ceftriaxone (39,5% of patients), and azithromycin (29,1% of patients). Antiviral medicines were used in 56,9% of patients⁶. Time matches with the study results and the first period of this research doesn't exist but during the entire epidemic, the situation in our country accompanied the situation in Western Europe, with significant setbacks.

Najmanja prevalencija prepisivanja antibiotika, od strane lekara u našoj Kovid ambulanti (43,1%), je bila u periodu od jula 2021. do maja 2022. godine. Taj period karakteriše veći obuhvat vakcinacijom, masovna upotreba antivirusika u primarnoj zdravstvenoj zaštiti, oboljenje sa blažom kliničkom slikom i tokom bolesti. U radu Cong W, Cheng HY, Stuart B, et al, se navodi da je u epidemiji COVID-19, stopa propisivanja antibiotika kod pacijenata sa COVID-19 bila u Kini 71.7%⁷.

Od juna 2022. godine do kraja oktobra 2022. godine epidemiju karakteriše smanjen intenzitet vakcinisanja, pojava izazivača manje osetljivih na vakcine, prisustvo više vrsta antivirusika, blaže kliničke slike obolelih i veći broj obolelih starijih od 65 godina. U tom periodu broj osoba kojima je prepisan antibiotik raste (72,93%) u odnosu na prethodni period. U drugom i trećem periodu antibiotici su više prepisivani osobama ženskog pola, najviše osobama starijim od 65 godina. Na početku epidemije najčešće su prepisivani cefalosporini (49%), azitromycin (29%), ostali makrolidi (17%), hinoloni (8%). U prvom periodu je i najveći procenat obolelih dobio kombinaciju dva antibiotika (8,3%) od ukupnog broja obolelih u tom periodu. Najčešća kombinacija je bila cefalosporin-hinolon (50%) od ukupnog broja osoba u tom periodu kojima su prepisana dva antibiotika, kombinacije cefalosporina i azitromycina, i drugih makrolida dobilo je 29,5%.

U drugom periodu udeo cefalopostina i dalje je dominantan (38%), povećao se udeo azitromycina (32%), hinolona (11%) i penicilina (8%). Kombinaciju od dva antibiotika dobilo je 4,3% obolelih u tom periodu. Prepisivana kombinacija je tada bila cefalosporin-hinolon (100%).

U trećem posmatranom periodu udeo azitromycina je najveći (46%), zastupljenost cefalosporina je i dalje veoma visoka (43%), a najznačajniji je pad udela hinolona (1%). Razlog u takvom izboru antibiotika je klinički tok oboljenja koji se prevashodno manifestovao na gornjim disajnim putevima. Kombinacija od dva antibiotika je tada najmanje korišćena (3,2% ukupnog broja obolelih), najčešće cefalosporin-hinolon (94%). U studijama koje su analizirale vrstu prepisivanih antibiotika u prvoj godini epidemije, najčešće prepisivani antibiotici su bili fluorohinoloni (20%), makrolidi (18,9%), penicilinski preparati (15%) i cefalosporini (15%). Najčešća kombinacija su kao i u našem istraživanju cefalosporin-fluorohinoloni i cefalosporin-makrolidni antibiotik⁸.

Prepisivanje antibiotika u Kovid ambulantama u Srbiji se razlikovalo, verovatno zbog različite dostupnosti Kovid bolnice i konsultanata (pneumoftiziologa i pulmologa) kojima su pripadale Kovid ambulante. Rezultati istraživanja u Kovid ambulanti u Kruševcu pokazuju da je početkom 2020. godine oko 50% pacijenata sa potvrđenom dijagnozom COVID-19 dobijala antibiotik, u oktobru 2021. antibiotik je dobijalo 65%, a antivirusike 9%, a početkom 2022. godine antibiotici su prepisani 64% pacijenata, a antivirusici 21% od ukupnog broja pacijenata lečenih u toj Kovid ambulanti.

The lowest prevalence of antibiotic prescription by physicians from our COVID clinic (43,1%) was during the period from July 2021 to May 2022. That period is characterized by greater vaccination coverage, massive use of antivirals in primary healthcare, disease with milder clinical presentation and course. Cong W, Cheng HY, Stuart B, et al report that in the COVID-19 epidemic, the rate of antibiotic prescribing in patients with COVID-19 in China was 71.7%⁷.

From June 2022 until the end of October 2022, the outbreak was characterized by the lesser intensity of vaccination, the appearance of the strains less sensitive to vaccines, the appearance of more antivirals, milder clinical presentations, and more diseased over the age of 65. At the time, the number of patients who were prescribed an antibiotic rose (72,93%) compared to the previous period. In the second and third periods, antibiotics were prescribed more to female patients, mostly those over 65. At the beginning of the outbreak, the most often prescribed antibiotics were cephalosporins (49%), azithromycin (29%), other macrolides (17%), and quinolones (8%). In the first period, the majority of patients got the combination of two antibiotics (8,3%) out of the total number of patients, at the time. The most common combination was cephalosporin-quinolone (50%), out of the total number of patients who were prescribed two antibiotics, at the time. A combination of cephalosporin and azithromycin, or other macrolides got 29,5% of patients, in total.

In the second period, the share of cephalosporins was still dominant (38%), the share of azithromycin also rose (32%), the share of quinolones was (11%), and penicillin (8%). A combination of two antibiotics was given to 4,3% of patients, at the time. The prescribed combination was cephalosporin-quinolone (100%), in this period.

In the third period, the share of azithromycin was the highest (46%), and the share of cephalosporins was still very high (43%), and the most important was the fall of quinolone share (1%). The reason for such a choice of antibiotic use was the clinical course of the disease, which mostly manifested in upper respiratory system symptoms. A combination of two antibiotics was the least used in this period (3,2% of the total number of patients), and the most common was cephalosporin-quinolone (94%). The studies that researched the sort of prescribed antibiotics, in the first year of the outbreak, found that the most commonly prescribed antibiotics were fluoroquinolones (20%), macrolides (18,9%), penicillin derivatives (15%), and cephalosporins (15%). The most common combination of antibiotics, as was the case in our study, was cephalosporin-fluoroquinolone and cephalosporin-macrolide⁸.

Prescription of antibiotics in the COVID outpatient clinics in Serbia differed, probably due to the different accessibility of COVID hospitals and consultants (pneumophthisiologists and pulmonologists) with whom COVID outpatient clinics cooperated. The results of the COVID outpatient clinic in Kruševac showed that at the beginning of 2020

ti⁹. Precizno poređenje ovih rezultata sa istraživanjem koje je sprovedeno u Kovid ambulanti Doma zdravlja Golubac nije moguće, jer nisu jasno definisani periodi prikazanih rezultata.

Autori većine studija ističu veći stepen prepisivanja antibiotika od preporučenih terapijskih protokola, vodiča dobre kliničke prakse i dokazanih bakterijskih infekcija (7,6–26%)^{8,9,10,11,12}, što sigurno utiče na razvoj bakterijske otpornosti na antibiotike. Osim upotrebe antibiotika koje su prepisivali lekari, veliki broj obolelih od COVID-19 je samoinicijativno upotrebljavao antibiotike. Jedna studija daje podatke da je 38% ispitanika uzimalo preventivno antibiotike da bi se zaštitili od infekcije COVID-19¹².

Ukupan broj pacijenata kojima je prepisan antivirusik, u Kovid ambulanti u ovom istraživanju, iznosi 855, što je 31,76% ukupnog broja pacijenata. Istovremeno je 551 pacijent dobio i antibiotik i antivirusik, a to je 20,46% ukupnog broja pacijenata. Antivirusici su uglavnom prepisivani u drugom i trećem period. Pretežno su prepisivani pacijentima starijim od 65 godina i više osobama ženskog od osoba muškog pola.

Upotreba antivirusika je rasla od jula 2021. godine. U periodu od jula 2021. godine do maja 2022. godine, 35,05% obolelih je dobilo antivirusik. U nastavku epidemije, sa povećanjem dostupnosti antivirusika u Kovid ambulantama, 59,80% obolelih je dobilo antivirusik. To je u skladu sa rezultatima studija u inostranstvu (68,7%)³, ali znatno više nego u studiji u našoj zemlji (21%)¹⁰. Najveći broj pacijenata dobio je Favipiravir (92% slučajeva). Ostali antivirusici imaju znatno manji udeo.

Zaključak

Upotreba antibiotika u lečenju obolelih od oboljenja COVID-19 je veća od preporučene protokolima i vodičima dobre kliničke prakse. Prepisivanje antibiotika u Kovid ambulanti Doma zdravlja Golubac se menjalo sa sticanjem novih saznanja o lečenju ovog oboljenja i epidemiološkom situacijom, i manje je nego na početku epidemije. Upotreba antivirusika je rasla sa povećanjem njihove dostupnosti i saznanja o efikasnosti u lečenju ovog oboljenja.

around 50% of patients, with the confirmed diagnosis of COVID-19, got an antibiotic. In October 2021, an antibiotic was prescribed to 65% of patients, and an antiviral to 9%. At the beginning of 2022, antibiotics were prescribed to 64% of patients and antivirals to 21% of the total number of treated patients in this COVID outpatient clinic⁹. A more precise comparison of these results with the results from the COVID outpatient clinic of PHC Golubac is not possible because the researched periods were not clearly defined.

The authors of the majority of studies emphasize the higher degree of antibiotic prescription, than recommended in the therapeutic protocols, guidelines, and conformed bacterial infections (7,6–26%)^{8,9,10,11,12}, which probably influenced bacterial resistance to antibiotics. Aside from antibiotics prescribed by physicians, a huge number of COVID-19 patients took the antibiotics on their own. One study shows that 38% of the participants took antibiotics as a form of prevention to protect themselves from the COVID-19 infection¹².

The total number of patients who were prescribed an antiviral in the COVID outpatient clinic, in this research, was 855 which makes up to 31,76% of the total number of patients. At the same time, 551 patients got an antibiotic and an antiviral, which makes up to 20,46% of the total number of patients. The antivirals were mostly prescribed in the second and third period. They were mostly prescribed to older patients, over the age of 65 and more to females than males.

The use of antivirals grew from July 2021. From July 2021 to May 2022, 35,05% of the diseased got an antiviral. In the further course of the outbreak, with an increased availability of antivirals in the COVID outpatient clinics, 59,80% of the diseased got them. This is in line with the results from the foreign studies (68,7%)³ but significantly more than in the study from our country (21%)¹⁰. The majority of the patients got Favipiravir (92% of cases). Other antivirals had a significantly lesser share.

Conclusion

The use of antibiotics in the treatment of COVID-19 was higher than recommended by protocols and guidelines. Prescription of antibiotics in the COVID outpatient clinic of Primary Healthcare Center Golubac changed with gaining new knowledge on the treatment of the disease and epidemiological situation, and it was less than at the beginning of the outbreak. The use of antivirals grew with an increase in their availability and knowledge of their efficacy in the treatment of the disease.

Reference/ Literatura

1. World Health Organization. WHO announces COVID-19 outbreak a pandemic. World Health Organization, Geneva, 2020. Available from: <https://reliefweb.int/report/world/who-announces-covid-19-outbreak-pandemic> [Accessed October 26, 2023]
2. IIoannidis JPA. Infection fatality rate of COVID-19 inferred from seroprevalence data. *Bull World Health Organ* 2021;99(1):19–33F.
3. Langford BJ, So M, Raybardhan S, Leung V, Soucy JPR, Westwood D, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. *Clin Microbiol Infect* 2021;27(4):520–31.
4. Ministarstvo zdravlja. Nacionalni vodič dobre kliničke prakse. Racionalna upotreba antibiotika. Beograd: Ministarstvo zdravlja Republike Srbije; 2018. Available at https://www.zdravlje.gov.rs/view_file.php?file_id=527&cache=sr
5. Akoglu, H. User's guide to correlation coefficients. *Turk J Emerg Med* 2018;18(3):91–3.
6. Chedid M, Waked R, Haddad E, Chetata N, Saliba G, Choucair J. Antibiotics in treatment of COVID-19 complications: a review of frequency, indications, and efficacy. *J Infect Public Health* 2021;14(5):570–6.
7. Cong W, Cheng HY, Stuart B, Liu B, Tang Y, Wang Y, Alhusein N, Wang H, Machundiya A, Lambert H. Prevalence of antibiotic prescribing in COVID-19 patients in China and other low- and middle-income countries during the pandemic (December 2019—March 2021): a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy*, 2023; 72(12), 2787-2794.
8. Milovanović J, Jotić A, Radin Z, Ćirković I. Rational use of antibiotics during the COVID-19 pandemic. *Srpski medicinski casopis Lekarske komore* 2021;2(4):399–408.
9. Punoševac DT, Vesić-Veškovic SB. Diagnosis and treatment of COVID-19 in primary healthcare. *Opšta medicina* 2022;28(1–2):1–7.
10. Giri M, Puri A, Wang T, Guo S. Comparison of clinical manifestations, pre-existing comorbidities, complications and treatment modalities in severe and non-severe COVID-19 patients: A systemic review and meta-analysis. *Sci Prog* 2021;104(1):368504211000906.
11. Gerver SM, Guy R, Wilson K, Thelwall S, Nsonwu O, Rooney G, et al. National surveillance of bacterial and fungal coinfection and secondary infection in COVID-19 patients in England: lessons from the first wave. *Clin Microbiol Infect* 2021;27(11):1658–65.
12. Barakat AM, Mohaseeb MM. Self-medication with antibiotics based on the theory of planned behavior among an Egyptian rural population during the era of COVID-19 pandemic. *Egyptian Journal of Community Medicine*, 2023; 40(1): 51-60.

Primljen - Received - 23.04.2023.

Ispravljen - Corrected - 12.12.2023.

Prihvaćen - Accepted - 20.12.2023.