RACIONALNA UPOTREBA ANTIBIOTIKA TOKOM PANDEMIJE KOVID-19 INFEKCIJE

PREGLEDNI RAD

REVIEW ARTICLE

RATIONAL USE OF ANTIBIOTICS DURING THE COVID-19 PANDEMIC

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SAŽETAK

Uvod/Cilj: Globalna pandemija izazvana SARS-KoV-2 virusom se odavno smatra vanrednom situacijom, gde broj slučajeva eksponencijalno raste, uprkos stalnim naporima da se infekcija suzbije. Iako je bolest KOVID-19 izazvana SARS-KoV-2 virusom, većini pacijenata se ordinira antibiotska terapija. Zabrinjavajuće je kakvi će biti dugoročni efekti ovakvo široke primene antibiotika na antimikrobnu rezistenciju. Cilj ovog rada je da se, na osnovu dostupne literature: utvrdi kakav je uticaj pandemije KOVID-19 oboljenja na upotrebu antibiotika u cilju lečenja; utvrdi kakva je globalna situacija rezistencije na antibiotike; identifikuju ključne oblasti u kojima bi bile potrebne hitne promene.

Metode: Sproveden je sistematski pregled aktuelne literature o upotrebi antibiotika u lečenju KOVID-19 infekcije kod pacijenata. Pretražene su publikacije u bazama podataka *PubMed* i *MEDLINE*, objavljene od marta 2020. do septembra 2021. godine.

Rezultati: Antibiotici su prepisivani kod između 76,8% i 87,8% pacijenata lečenih od KOVID-19 oboljenja. Antibiotici su se u manjoj meri prepisivali deci u odnosu na odrasle (38,5%, u odnosu na 83,4%). Najčešće ordinirani antibiotici su bili fluorohinoloni (20%), makrolidi (18,9%), β-laktamski antibiotici (15,0%), i cefalosporini (15,0%). Samostalno uzimanje antibiotika je identifikovano kao jedan od bitnih faktora koji doprinose antimikrobnoj rezistenciji tokom KOVID-19 pandemije.

Zaključak: Uticaj pandemije KOVID-19 oboljenja na globalnu antimikrobnu rezistenciju je još uvek nepoznat i verovatno će biti neravnomerno raspoređen u opštoj populaciji. Iako su kod pacijenata sa KOVID-19 oboljenjem korišćeni različiti antibiotici, njihova uloga i potreba za njihovom primenom u lečenju ove infekcije se još utvrđuje. Za sada nema pouzdanih podataka da primena antibiotika, u slučajevima KOVID-19 infekcija koje nisu udružene sa bakterijskim infekcijama, ima efekat na tok bolesti i mortalitet.

Ključne reči: antibiotici, KOVID-19, antimikrobna rezistencija, bakterije

ABSTRACT

Introduction/Aim: The global COVID-19 pandemic has long been considered an emergency, with the number of cases growing exponentially, despite constant efforts to control the infection. Although the disease is caused by the SARS-CoV-2 virus, most patients are treated with antibiotic therapy. The long-term effects of such broad antibiotics use on antimicrobial resistance are still unknown and are a matter for concern. The aim of this paper is: to determine, based on the available literature, the impact of the COVID-19 pandemic on the use of antibiotics; to determine the global situation regarding antimicrobial resistance; to identify key areas where urgent changes are needed.

Methods: A systematic review of the current literature on the use of antibiotics in COVID-19 treatment was conducted. The PubMed and MEDLINE databases were searched for papers published between March 2020 and September 2021.

Results: Between 76.8% and 87.8% of patients with COVID-19 were treated with antibiotics. Antibiotics were less frequently prescribed to children, as compared to adults (38.5%, compared to 83.4%). The most commonly administered antibiotics were fluoroquinolones (20.0%), macrolides (18.9%), β-lactam antibiotics (15.0%), and cephalosporins (15.0%). Self-medication with antibiotics to prevent and treat COVID-19 has been identified as one of the important factors contributing to antimicrobial resistance.

Conclusion: The impact of COVID-19 on global antimicrobial resistance is still unknown and is likely to be unevenly distributed in the general population. Although various antibiotics have been used to treat patients with COVID-19, their role and the need for their application in the treatment of this infection remains to be determined. For now, there are no reliable data as to whether the use of antibiotics in COVID-19 cases without associated bacterial infections has any effect on the course of the disease and mortality.

Key words: antibiotics, COVID-19, antimicrobial resistance, bacteria

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UVOD

Globalna pandemija izazvana SARS-KoV-2 virusom se odavno smatra vanrednom situacijom bez presedana. Svetska zdravstvena organizacija (SZO) je, 30. januara 2020. godine, zbog porasta infekcija izazvanih SARS-KoV-2 virusom, zvanično proglasila vanredno stanje u javnom zdravlju na međunarodnom nivou, dok je 11. marta 2020. godine proglašena pandemija [1]. Uprkos stalnim naporima da se suzbije širenje infekcije, broj slučajeva eksponencijalno raste. Postoji velika varijabilnost u kliničkim karakteristikama bolesti, od blagih simptoma infekcije u gornjem respiratornom traktu, do životno ugrožavajućih infekcija donjeg respiratornog trakta. Skoro 80,0% pacijenata je asimptomatsko ili ima blagu formu bolesti, 15,0% ima tešku formu bolesti i zahteva oksigenaciju, a 5,0% ima životno ugrožavajuću formu bolesti i zahteva mehaničku ventilaciju. Mortalitet od ove bolesti iznosi 3,4% [2]. Iako je klinička slika bolesti izazavana virusom SARS-KoV-2, većini pacijenata je ordinirana antibiotska terapija, u čak 76,8% slučajeva, dok su antivirusni lekovi ordinirani u 68,7% slučajeva [3]. S obzirom da je i pre početka pandemije bila detektovana povećana rezistencija bakterija na raspoložive antibiotike [4], zabrinjavajuće je kakvi će biti dugoročni ishodi ovako široke primene antibiotika na svetskom nivou.

Cilj ovog rada je da se, na osnovu dostupne literature: utvrdi kakav je uticaj pandemije KOVID-19 oboljenja na upotrebu antibiotika u cilju lečenja; utvrdi kakva je globalna situacija rezistencije na antibiotike; identifikuju ključne oblasti u kojima bi bile potrebne hitne promene.

METODE

Sproveden je sistematski pregled aktuelne literature o upotrebi antibiotika u lečenju KOVID-19 infekcije kod pacijenata. Pretražene su publikacije u bazama podataka *PubMed* i *MEDLINE,* objavljene od marta 2020. do septembra 2021. godine. Uključeni su svi radovi na engleskom jeziku, kao i retrospektivne analize, sistematski pregledi i meta-analize. Termini: „antibiotici", „KOVID-19", "SARS-KoV-2", „ terapija", „ bakterijska rezistencija", „antimikrobna rezistencija", „antibakterijski agensi", „rezistencija na lekove" su korišćeni za identifikaciju relevantnih članaka. Izveštaji o prikazima slučajevima i istraživanjima sprovedenim na životinjama su isključeni, kao i duplirane reference.

IZBOR TERAPIJE KOD PACIJENATA SA KOVID-19 INFEKCIJOM

Nacionalna multicentrična studija, sprovedena od strane Bendala Estrade i saradnika, obuhvatila je podatke 13.932 registrovana pacijenta lečena od KOVID-19 infekcije u

INTRODUCTION

The global pandemic caused by the SARS-CoV-2 virus has long been considered an unprecedented crisis. On January 30, 2020, the World Health Organization (WHO) officially declared an international state of emergency in public health, due to the increase in infections caused by the SARS-CoV-2 virus, while the pandemic was declared on March 11, 2020 [1]. Despite constant efforts to curb the spread of the infection, the number of cases is growing exponentially. There is great variability in the clinical characteristics of the disease, from mild symptoms of infection in the upper respiratory tract, to life-threatening infections of the lower respiratory tract. Almost 80.0% of patients are asymptomatic or have a mild form of the disease, 15.0% have a severe form of the disease and require oxygenation, while 5.0% have a life-threatening form of the disease and require mechanical ventilation. Disease mortality is 3.4% [2]. Although the clinical symptoms are caused by the SARS-CoV-2 virus, most patients were prescribed antibiotic therapy, in 76.8% of cases, while antiviral drugs were prescribed in 68.7% of cases [3]. Increased bacterial resistance to available antibiotics was detected even before the pandemic [4]. Therefore, the question of what the future long-term outcomes of such widespread use of antibiotics will be is a matter for concern.

The aim of this paper is: to determine, based on the available literature, the impact of the COVID-19 pandemic on the use of antibiotics; to determine the global situation regarding antimicrobial resistance; to identify key areas where urgent changes are needed.

METHODS

A systematic review of the current literature on the use of antibiotics in COVID-19 treatment was conducted. The PubMed and MEDLINE databases were searched for papers published between March 2020 and September 2021. All papers in English were included, as well as retrospective analyses, systematic reviews, and meta-analyses. The terms: "antibiotics", "COVID-19", "SARS-CoV-2", "treatment", "bacterial resistance ", "antimicrobial resistance", "anti-bacterial agents", "drug resistance", were used to identify relevant articles. Reports of case reports and animal studies were excluded, as well as duplicate references.

TREATMENT OPTIONS IN COVID-19 PATIENTS

A national multi-centric study conducted by Bendala Estrada et al. included data on 13,932 registered patients treated for COVID-19 in Spain [5]. Antibiotics were prescribed to 12,238 (87.8%) patients, while only 1,498 (10.8%) patients did not receive antibiotic

Španiji [5]. Antibiotici su prepisivani kod 12.238 (87,8%) pacijenata, dok samo 1.498 (10,8%) pacijenata nije dobilo antibiotsku terapiju. Meta-analiza 41 studije iz 11 zemalja, koja je obuhvatila 16.495 pacijenata, uporedila je modalitete terapije kod pacijenata sa teškim i drugim formama (lakši i srednje-teški oblici bolesti) [3]. Većina pacijenata je primala antibiotsku terapiju (76,8%, 95,0% *CI*: 70,2% – 83,5%), potom antivirusnu terapiju (68,7%, 95% *CI*: 53,6% – 83,8%), kiseoničku terapiju (55,5%, 95,% *CI*: 41,9% – 69,1%), kao i kortikosteroidnu terapiju (35,4%, 95,0% *CI*: 27,4% – 43,5%). U poređenju sa pacijentima sa manje teškim formama bolesti, pacijenti sa teškim formama bolesti su imali veću verovatnoću da budu lečeni antibiotskom terapijom (*OR*=6, 95,0% *CI*: 3,3 – 10,7; p<0,00001) i antivirusnom terapijom (*OR*= 2,2, 95,0% *CI*: 1,4 – 3,3; p=0,0003). Nije pronađena statistički značajna razlika u upotrebi kiseoničke terapije između grupa (*p*=0,710). Langford i saradnici [6] su sproveli još jednu meta-analizu na 154 studije i na dostupnim podacima o antibiotskoj terapiji kod 30.623 pacijenata. Prevalencija prepisivanja antibiotika nije mnogo odstupala od prethodno prijavljene, i iznosila je 74,6% (95,0% *CI*: 68,3% – 80,0%). Antibiotici su se u manjoj meri prepisivali deci u odnosu na odrasle (38,5% u odnosu na 83,4%). Što je pacijent bio stariji, postojala je veća verovatnoća da mu se prepiše antibiotska terapija (*OR*=1.5 na 10 godina starosti, 95,0% *CI*: 1,2 – 1,8). Takođe, antibiotici su ordinirani u zavisnosti od težine kliničke slike. Najmanje su prepisivani 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%).

U Srbiji za sada nema podataka o bakterijskoj rezistenciji na antibiotike kod KOVID-19 pozitivnih pacijenata.

IZBOR ANTIBIOTIKA KOD PACIJENATA SA KOVID-19 INFEKCIJOM

Najčešće ordinirani antibiotici su bili fluorohinoloni (20,0%), makrolidi (18,9%), β-laktamski antibiotici (15,0%) i cefalosporini (15,0%) [6]. Kombinovana antibiotska terapija je najčešće korišćenja kod pacijenata sa teškom kliničkom slikom, pretežno za terapiju pneumonije. Najučestalije kombinacije su sadržale cefalosporinske, fluorohinolonske i makrolidne antibiotike [7].

Upotreba antibiotika je široko varirala u različitim delovima sveta. U Evropi je iznosila 63.1% (95,0% *CI*: 41.7% – 80.4%), u Severnoj Americi je bila 64,8% (95,0% *CI*: 54% – 74,2%), u Kini je iznosila 76,2% (95,0% *CI*: 66,8% – 82,3%), na Srednjem Istoku je bila 86.0% (95,0% *CI*: 77,4 % – 91,7%), dok je u Istočnoj i Jugoistočnoj Aziji iznosila 87,5% (95,0% *CI*: 47,8% – 98,2%). U Evropi su najviše ordinirani β-laktamski antibitici,

therapy. Meta-analysis of 41 studies from 11 countries involving 16,495 patients compared treatment modalities in patients with severe and other forms (mild to moderate) [3]. Most patients received antibiotic therapy (76.8%, 95.0% CI: 70.2% – 83.5%), followed by antiviral therapy (68.7%, 95.0% CI: 53.6% – 83.8%), oxygen therapy (55.5%, 95% CI: 41.9% – 69.1%), and corticosteroid therapy (35.4%, 95.0% CI: 27.4% – 43.5%) Compared to patients with less severe forms of the disease, patients with severe forms of the disease were more likely to be treated with antibiotic therapy (OR = 6, 95.0% CI: 3.4 – 10.7, $p < 0.00001$) and antiviral therapy (OR = 2.2, 95.0% CI: 1.4–3.3, $p = 0.0003$). No statistically significant difference was found in the use of oxygen therapy between groups ($p = 0.710$). Langford et al. [6] conducted another meta-analysis of 154 studies and the available data on antibiotic therapy in 30,623 patients. The prevalence of prescribing antibiotics did not considerably vary from what had been reported previously, and it was 74.6% (95.0% CI: 68.3% – 80.0%). Antibiotics were prescribed to children to a lesser extent than to adults (38.5%, compared to 83.4%). The older the patient, the more likely he/she was to be prescribed antibiotic therapy (OR 1.5 per 10 years of age, 95.0% CI: 1.2 – 1.8). Also, antibiotics were prescribed depending on the severity of clinical presentation. Antibiotics were less prescribed in patients who were not hospitalized (59.3%) as compared to those who were hospitalized with a mild or moderate form of the disease (74.8%), and to those in intensive care (86.4%).

Thus far, there are no data on antimicrobial resistance in COVID-19 positive patients, in Serbia.

ANTIBIOTIC OPTIONS IN COVID-19 PATIENTS

The most commonly administered antibiotics were fluoroquinolones (20.0%), macrolides (18.9%), β-lactam antibiotics (15.0%) and cephalosporins (15.0%) [6]. A combination of antibiotics was most commonly used in patients with the severe form of the disease, predominantly for the treatment of pneumonia. The most common combinations contained cephalosporins, fluoroquinolone, and macrolide antibiotics [7].

The use of antibiotics varied widely in different parts of the world. In Europe it was 63.1% (95.0% CI: 41.7% – 80.4%), in North America it amounted to 64.8% (95.0% CI: 54.0% – 74.2%), in China it was 76.2% (95.0% CI: 66.8% – 82.3%), in the Middle East it amounted to 86.0% (95.0% CI: 77.4% – 91.7%), while in East and Southeast Asia it was 87.5% (95.0% CI: 47.8% – 98.2%). In Europe, β-lactam antibiotics, macrolides and cephalosporins were the ones most commonly prescribed, while in North America macrolides, cephalosporins and β-lactam antibiotics were the ones used the most.

makrolidi i cefalosporini, a u Severnoj Americi makrolidi, cefalosporini i β-laktamski antibiotici. U Kini su pacijentima najčešće prepisivani fluorohinoloni, β-laktamski antibiotici i cefalosporini, dok su u Istočnoj i Jugoistočnoj Aziji najviše korišćeni cefalosporini, makrolidi i fluorohinoloni [6].

U prvih nekoliko meseci pandemije, proširena je upotreba azitromicina u terapiji KOVID-19 infekcije. *In vitro* studije su iznele dokaze da azitromicin ima antiviralna svojstva protiv mnogih respiratornih virusa (uključujući rinovirus, SARS-KoV-2 virus i Zika virus) [8]. Takođe, dokazana su njegova imunomodulatorna svojstva, što je donekle teorijski opravdavalo njegovu primenu u terapiji KOVID-19 oboljenja [9]. Kasnije studije o primeni u kliničkoj praksi nisu opravdale njegovu primenu. Poređenjem populacije koja je primala azitromicin sa populacijom pacijenata koja je primala simptomatsku terapiju, zaključeno je da nije bilo efekta azitromicina ni na pogoršanje odnosno poboljšanje stanja, ni na broj dana hospitalizacije, niti na stepen mortaliteta, bilo da se radilo o pacijentima na kućnom ili bolničkom lečenju [10- 2]. Zaključak je da azitromicin treba prepisivati samo pacijentima kod kojih postoji jasna indikacija za njegovo davanje, posebno ukoliko se radi o hospitalizovanim pacijentima.

Iako su kod pacijenata sa KOVID-19 oboljenjem korišćeni različiti antibiotici, njihova uloga i potreba za njihovom primenom u lečenju ove infekcije se još utvrđuje. Za sada nema pouzdanih podataka da primena antibiotika u slučajevima KOVID-19 infekcije bez pridruženih bakterijskih infekcija ima uticaja na tok bolesti i mortalitet [10]. Zaključeno je da kod lakših formi bolesti treba izbegavati antibiotike u terapiji, jer ne utiču na progresiju bolesti, mortalitet i dužinu hospitalizacije [13]. Kliničari treba da izbegavaju produženu i neodgovarajuću upotrebu antimikrobnih lekova, koji mogu da izazovu antimikrobnu rezistenciju i smanjenje efikasnosti ovih lekova.

MIKROBIOLOGIJA KOINFEKCIJA I SUPERINFEKCIJA KOD PACIJENATA OBOLELIH OD KOVID-19 INFEKCIJE

U cilju utvrđivanja stepena prisustva bakterijske ili mikotičke koinfekcije ili sekundarne infekcije, u Velikoj Britaniji je sprovedena nacionalna retrospektivna studija, koja je obuhvatila sve pacijente sa laboratorijski potvrđenom KOVID-19 infekcijom, u periodu od 1. januara do 2. juna 2020. godine (221.134 pacijenta) [14]. Koinfekcija je podrazumevala izolovanje uzročnika dan pre, na dan ili dan posle potvrđivanja infekcije SARS-KoV-2 virusom. Sekundarna infekcija je podrazumevala izolovanje uzročnika u periodu od dva do 21 dana posle potvrđivanja infekcije SARS-KoV-2 virusom. Prisustvo

In China, patients were most often prescribed fluoroquinolones, β-lactam antibiotics, and cephalosporins, while in East and Southeast Asia, cephalosporins, macrolides, and fluoroquinolones were the ones most commonly used [6].

In the first few months of the pandemic, the use of azithromycin in the treatment of COVID-19 infections was expanded. In vitro studies provided evidence of azithromycin's antiviral properties against many respiratory viruses (including the rhinovirus, the SARS-CoV-2 virus, and the Zika virus) [8]. Also, its immunomodulatory properties had been proven, which to some extent, theoretically justified its use in the treatment of COVID-19 [9]. Subsequent studies on its application in clinical practice have not justified its use. A comparison between the population which had been receiving azithromycin and the population of patients which had been receiving symptomatic therapy revealed that there was no effect of this drug on the worsening or improving of the patient's condition, on the number of days of hospitalization, or on the mortality rate, regardless of whether the patients had been at home or hospitalized [10-12]. The conclusion was that azithromycin should be prescribed only when there was a clear indication for its administration, especially in the case of hospitalized patients.

Although various antibiotics have been used in treating patients with COVID-19, their role and the need for their use in the treatment of this infection is still being examined. For now, there are no reliable data proving that the use of antibiotics in cases of COVID-19 without associated bacterial infections has any effect on the course of the disease and mortality [10]. In milder forms of the disease, antibiotics should be avoided in therapy, because they do not affect the progression of the disease, mortality and length of hospitalization [13]. Clinicians should avoid prolonged and inappropriate use of antimicrobial drugs that can cause antimicrobial resistance and reduce the efficacy of these drugs.

MICROBIOLOGY OF CO-INFECTION AND SUPERINFECTION IN COVID-19 PATIENTS

For the purpose of determining the extent of bacterial or fungal co-infection or secondary infection, a national retrospective study was conducted in the UK, which included all patients with laboratory-confirmed COVID-19, between January 1 and June 2, 2020 (221,134 patients) [14]. Co-infection involved isolating the causative agent the day before, on the day, or one day after the confirmation of SARS-CoV-2 infection. Secondary infection involved the isolation of the causative agent 2 to 21 days after confirmation of the SARS-CoV-2 infection. The presence of infection was determined by isolating the causative agent from blood samples or

infekcije se utvrđivalo izolovanjem uzročnika u uzorcima krvi ili uzorcima iz respiratornog trakta. Samo 2.279 (1,0%) pacijenata je imalo potvrđenu koinfekciju ili sekundarnu infekciju. Sekundarne infekcije su bile češće od koinfekcija (61,4% naspram 38,6%; 95,0% *CI*: 36,6% – 40,6%). Većina ovih infekcija je izolovana iz uzoraka krvi (u 66,0% slučajeva), odnosno kod 0,7% svih slučajeva KOVID-19 oboljenja. Bakterijemija i sepsa su bile 6,5 puta češće nego respiratorne koinfekcije i dva puta češće od sekundarnih respiratornih infekcija. Pacijenti koji su imali koinfekcije i sekundarne infekcije su češće bili stariji (≥ 40 godina) i muškog pola ($p < 0,001$). Smrtnost kod pacijenata sa koinfekcijama/sekundarnim infekcijama je bila značajno veća u odnosu na pacijente bez ovih infekcija (23,0% i 26,6%, redom, u odnosu na 7,6%). Najčešće izolovane hematogene bakerije su bile *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterococcus faecium*, kao i nepiogeni streptokoki, dok su najčešće izolovane respiratorne bakterije bile *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus*, kao i *Klebsiella pneumoniae*. Izazivač najčešćih respiratornih mikotičkih infekcija bio je *Aspergillus fumigatus*, a izazivač najčešćih hematogenih infekcija bila je *Candida albicans*.

Ukoliko posmatramo samo bakterijski izazvane plućne koinfekcije/superinfekcije, prevalencija se kreće od 8,6% do 16,0% [6,15-17]. Razlike postoje verovatno zbog prethodne primene antibiotika, lošeg kvaliteta uzoraka, varijacija u interpretaciji rasta uzoraka, kao i zbog poteškoća u kultivaciji izolovanih mikroorganizama [18]. Prevalencija koinfekcija/sekundarnih infekcija je drastično rasla kod pacijenata u intenzivnoj nezi (do 33,0%), pri čemu je primena antibiotika pre uzorkovanja iznosila 28,0% - 79,0% [19].

Španski autori [17] su na 1.251 uzorku iz respiratornog trakta došli do zaključka da su bakterijske plućne koinfekcije u najvećem broju slučajeva bile monomikrobne (92,5%). Najčešće izolovane bakterije su bile *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae/Klebsiella aerogenes,* kao i *Escherichia coli*. U 10,8% uzoraka radilo se o multirezistentnim retkim bakterijama (*Achromobacter spp*., *Burkholderia spp*., *Stenotrophomonas spp*., *Chryseobacterium spp*., *Corynebacterium spp*.). Klinički izolovani izolati su bili veoma slični izolatima kod virusnih pneumonija koje nisu udružene sa KOVID-19 infekcijom [20].

Kada govorimo o sekundarnim plućnim infekcijama, rezultati sistematskog pregleda literature, koji je obuhvatio 5.047 hospitalizovanih pacijenata sa pneumonijama povezanim sa KOVID-19 infekcijom, 49 studija ukazuje na to da su najčešće izolovani bakterijski uzročnici bili *Pseudomonas aeruginosa* (21,1%), *Klebsiella species* (17,2%), *Staphylococcus aureus*

samples taken from the respiratory tract. Only 2,279 (1.0%) patients had a confirmed co-infection or secondary infection. Secondary infections were more common than co-infections (61.4% vs. 38.6%, 95.0% *CI*: 36.56% – 40.60%). Most of these infections were isolated from blood samples (in 66.0% of cases), i.e., in 0.7% of all COVID-19 cases. Bacteremia and sepsis were 6.5 times more common than respiratory co-infections and twice as common as secondary respiratory infections. Patients who had co-infections and secondary infections were more often older (≥ 40 years) and male (p <0.001). Mortality in patients with coinfections/secondary infections was significantly higher compared to patients without such infections (23.0% and 26.6%, respectively, compared to 7.6%). The most commonly isolated hematogenous bacteria were *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterococcus faecium*, and non-pyogenic streptococci, while the most commonly isolated respiratory bacteria were *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. The most common respiratory mycotic infections were caused by *Aspergillus fumigatus*, while the most common hematogenous infections were caused by *Candida albicans*.

If only bacterially induced pulmonary coinfections/superinfections are taken into consideration, the prevalence ranges from 8.6% to 16.0% [6,15-17]. The differences probably exist due to previous antibiotic administration, poor sample quality, variations in the interpretation of sample growth, and challenges associated with cultivating microorganisms [18]. The prevalence of coinfections/secondary infections drastically increased in patients in intensive care (up to 33.0%), with the antibiotics use before sampling amounting to 28.0% - 79.0% [19].

Spanish authors [17] found, based on 1,251 samples taken from the respiratory tract, that bacterial pulmonary co-infections were, in most cases, monomicrobial (92.5%). The most commonly isolated bacteria were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae/Klebsiella aerogenes*, and *Escherichia coli*. In 10.8% of the samples multidrug-resistant rare bacteria (*Achromobacter spp*., *Burkholderia spp*., *Stenotrophomonas spp*., *Chryseobacterium spp*., *Corynebacterium spp*.) were isolated. Clinical isolates were very similar to the isolates in viral pneumonias not associated with COVID-19 [20].

When it comes to secondary lung infections, the results of a systematic review, which included 5,047 hospitalized patients with COVID-19-associated pneumonia in 49 studies, indicated that the most commonly isolated bacterial pathogens were *Pseudomonas aeruginosa* (21.1%), *Klebsiella species* (17.2%), *Staphylococcus aureus* (13.5%), *Escherichia coli* (10.4%), and *Stenotrophomonas*

(13,5%), *Escherichia coli* (10,4%), kao i *Stenotrophomonas maltophilia* (3,1%). Incidencija sekundarne mikotičke infekcije iznosila je 6,3%. Mikotičke infekcije su bile izazvane predominantno gljivicama iz roda *Aspergillus*, gde je najčešće bio izolovan *Aspergillus fumigatus*. Druge, ređe izolovane gljivice, bile su takođe iz roda *Aspergillus* (*Aspergillus flavus*, *Aspergillus calidoustus*, *Aspergillus citrinoterreus*, *Aspergillus niger*, *Aspergillus terreus*, *Aspergillus versicolor*), ali i gljivice *Mucor species*, *Fusarium proliferatum* i *Pneumocystis jirovecii* [16]. Mikotičke infekcije su češće detektovane kod azijske nego kod evropske populacije pacijenata sa KOVID-19 oboljenjem [21]. Kod pacijenata sa mikotičkim sekundarnim infekcijama, mortalitet je iznosio 0,2% i bio je značajno veći kod osoba hospitalizovanih u jedinicama intenzivne nege nego kod pacijenata u mešanoj bolničkoj populaciji (0,4% u odnosu na 0,1%) [21].

SAMOSTALNO UZIMANJE ANTIBIOTIKA U DOBA KOVID-19 INFEKCIJE

Samostalno uzimanje antibiotika je identifikovano kao jedan od bitnih faktora koji doprinose antimikrobnj rezistenciji. Ovo je čest problem čak i u zemljama sa strogim propisima i naprednim modelima zdravstvene nege [22-24]. Samolečenje antibioticima je definisano kao neprikladna i iracionalna upotreba antibiotika, gde osobe samostalno leče svoje simptome ili bolest bez pregleda lekara, ordinirane terapije i nadzora [25].

Pandemija je značajno uticala na mentalno zdravlje u opštoj populaciji, rezultirajući rastom nivoa stresa, straha, anksioznosti i depresije [26]. Shodno savetima nadležnih organa, ljudi su uzeli na sebe da se zaštite od infekcije. To je dovelo i do nekih ekstremnih oblika ponašanja, širenja dezinformacija i pogrešnog tumačenja saveta lekarske profesije. U studiji koju su sproveli Đang i saradnici na 2,217 ispitanika iz Australije [27], 19,5% ispitanika je uzimalo antibiotike preventivno, da bi se zaštitili od infekcije SARS-KoV-2 virusom. Zabeležen je viši nivo stresa, prisustvo anksioznosti, straha od infekcije, i sveukupna zabrinutost kod ispitanika koji su uzimali antibiotike u odnosu na one koji nisu. Takođe, ti ispitanici nisu bili dovoljno informisani o samim antibioticima. Veći broj pacijenata je smatrao da antibiotici leče i virusne infekcije (34,1%) i nije znao da antibiotici leče samo bakterijske infekcije (25,6%). Antibiotike je 35,6% pacijenata uzimalo kako bi izlečili grip ili prehladu. Ove lekove su dobijali od prijatelja ili rodbine (17,9%), od svog lekara (47,1%) ili su koristili ono što im je ostalo od ranije (23,2%). Zapaženo je da su ispitanici koji su zloupotrebljavali antibiotike bili višeg obrazovanja, da su češće bili edukovani za neki rad u zdravstvu, i da su znali razliku između virusne i bakterijske infekcije, iako su manje znali o dejstvu antibiotika tokom

maltophilia (3.1%). The incidence of secondary mycotic infection was 6.3%. Mycotic infections were caused predominantly by fungi belonging to the *Aspergillus* genus, with *Aspergillus fumigatus* being the species most commonly isolated. Other less commonly isolated fungi were *Aspergillus flavus*, *Aspergillus calidoustus*, *Aspergillus citrinoterreus, Aspergillus niger*, *Aspergillus terreus*, *Aspergillus versicolor*, *Mucor species*, *Fusarium proliferatum*, and *Pneumocystis jirovecii* [16]. Mycotic infections were more frequently detected in the Asian population than in the European population of COVID-19 patients [21]. In patients with secondary mycotic infections, mortality was 0.2%. It was significantly higher in persons hospitalized in the intensive care units than in the mixed hospital population (0.4% vs. 0.2%) [21].

SELF-MEDICATION WITH ANTIBIOTICS IN THE COVID-19 ERA

Self-medication with antibiotics has been identified as one of the important factors contributing to antimicrobial resistance. Even in countries with strict regulations and advanced models of health care, this is a common problem [22-24]. Self-medication with antibiotics is defined as the inappropriate and irrational use of antibiotics, where individuals self-treat their symptoms or illness without a physician's examination, prescribed therapy, or supervision [25].

The pandemic has significantly affected mental health in the general population, resulting in an increase in the levels of stress, fear, anxiety and depression [26]. This has also led to some extreme forms of behavior, to the spreading of misinformation, and to the misinterpreting of the advice given by the medical profession. In a study conducted by Zhang et al. on 2,217 subjects from Australia [27], 19.5% of subjects took antibiotics to prevent getting infected with the SARS-CoV-2 virus. Higher levels of stress, the presence of anxiety, fear of infection, and overall concern were noted in subjects who took antibiotics, as compared to those who did not. Also, these subjects were not sufficiently informed about the antibiotics themselves. A larger number of patients believed that antibiotics treat viral infections (34.1%) and did not know that antibiotics only treat bacterial infections (25.6%). A total of 35.6% of patients used antibiotics to cure the flu or a cold. They obtained antibiotics from friends or relatives (17.9%), from their doctor (47.1%), or used what they had left from before (23.2%). It was noted that subjects who self-medicated were more educated and more often worked in a health-related profession. They knew the difference between viral and bacterial infections, although they knew less about the effects of antibiotics during viral and bacterial infections. This leaves

virusnih i bakterijskih infekcija. Ovo ostavlja prostora za mogućnost edukacije ovog dela populacije o tačnim načinima dejstva i upotrebi antibiotika u lečenju.

U sistematskom pregledu literature koji su sproveli Kvinčo-Lopez i saradnici [28], najčešće korišćeni antibiotici za prevenciju i samostalno lečenje KOVID-19 oboljenja su bili azitromicin, penicilin i amoksicilin. Prema podacima iz te studije, pre antibiotika su uzimani vitamini i drugi suplementi, nesteroidni antiinflamatorni lekovi, acetaminofen, hidroksihlorokin i ivermektin.

TELEMEDICINA I ORDINIRANJE ANTIBIOTIKA U DOBA KOVID-19 INFEKCIJE

Tokom pandemije, zemlje sa bolje organizovanim zdravstvenim sistemima su prelazile na telemedicinu i virtuelne preglede pacijenata, u cilju očuvanja zdravstvenih resursa i ljudstva, ali i smanjenja rizika od izlaganja infekciji i zaražavanja SARS-KoV-2 virusom [29]. Iako sprovođenje telemedicinskih lekarskih pregleda nije bilo bez svojih izazova, predstavljalo je neophodan korak ka premošćavanju perioda bez vakcina.

Postojale su neke razlike između dečije i odrasle populacije. Kod odraslih, antibiotici su se ređe prepisivali tokom telemedicinskih pregleda, nego tokom pregleda u ordinacijama. Najčešće stanje koje je lečeno antibioticima je bio akutni faringitis (21,2% pri telemedicinskim pregledima i 39,7% pri posetama lekaru; p <0,001). Ukoliko se radilo o drugim infekcijama respiratornog trakta, prepisivanje antibiotika je bilo značajno ređe (1,6% u odnosu na 19,9%; p <0,001). Prepisivani su antibiotici prema aktuelnim preporukama (kod faringitisa u 96,4% naspram 94,4%, a kod drugih infekcija gornjeg respiratornog trakta 96,3% naspram 74,0%) [30]. U dečijoj populaciji dešavalo se suprotno. Veća je verovatnoća bila da deca dobiju antibiotik tokom telemedicinskih pregleda (52,0%) nego tokom poseta hitnoj službi (42,0%) ili odabranom pedijatru (31,0%). Antibiotici su prepisivani po aktuelnim preporukama kod 92,5% telemedicinskih pregleda, i kod 90,7% pregleda u ordinacijama (p = 0,004) [31,32].

ANTIMIKROBNA REZISTENCIJA TOKOM PANDEMIJE KOVID-19 INFEKCIJE

Antimikrobna rezistencija, koja je bila zdravstveni problem i pre pandemije, sigurno će postati još više zabrinjavajuća u narednom periodu. Kako smo već naveli u prethodnim odeljcima, pandemija je gotovo potpuno uništila odgovorno ordiniranje antibioticima i znatno povećala njihovu upotrebu na svetskom nivou. Pored toga, stalna upotreba sredstava za dezinfekciju dovodi do formiranja sredine koja favorizuje neke mikrobne fenotipove, kao i do razvijanja rezistencije pojedinih antimikrobnih agenasa [33]. Te subpopulacije mikroba,

room for the possibility of educating this part of the population on the use of antibiotics in treatment and on the exact ways that antibiotics act.

In a systematic review of literature conducted by Quincho-Lopez et al. [28], the most commonly used antibiotics for the prevention and self-medication of COVID-19 were azithromycin, penicillin, and amoxicillin. According to the data from that study, vitamins and other supplements, non-steroidal anti-inflammatory drugs, acetaminophen, hydroxychloroquine and ivermectin were taken before the antibiotics.

TELEMEDICINE AND THE ADMINISTRATION OF ANTIBIOTICS IN THE AGE OF COVID-19

During the pandemic, countries with better organized healthcare systems switched to telemedicine and virtual patient examinations, in order to preserve health resources and staff, as well as to reduce the risk of exposure and infection with the SARS-CoV-2 virus [29]. Although conducting telemedicine visits is not without its challenges, it was a necessary step in overcoming the period when there were still no vaccines available.

There were some differences between the pediatric and adult population. In adults, antibiotics were prescribed less often during telemedicine visits than during office examinations. The most common condition treated with antibiotics was acute pharyngitis (21.2% during telemedicine visits and 39.7% during doctor visits; p < 0.001). In cases of other respiratory tract infections, antibiotic prescribing was significantly less frequent (1.6% compared to 19.9%; p < 0.001). Antibiotics were prescribed according to current recommendations (in pharyngitis in 96.4% versus 94.4%, and in other infections of the upper respiratory tract 96.3% versus 74.0%) [30]. The opposite happened in the pediatric population. Children were more likely to receive antibiotics during telemedicine visits (52.0%) than during emergency room visits (42.0%) or visits to their pediatrician (31.0%). Antibiotics were prescribed according to current recommendations in 92.5% of telemedicine visits, and in 90.7% of office examinations (p = 0.004) [31,32].

ANTIMICROBIAL RESISTANCE DURING THE COVID-19 PANDEMIC

Antimicrobial resistance, which had been a health issue even before the pandemic, will definitely become an even greater cause for concern in the upcoming period. As we have already stated in the previous sections, the pandemic has almost completely destroyed the stewardship of antibiotics and single-handedly increased their use worldwide. In addition, the constant use of disinfectants has led to the formation of an environment that favors some microbial phenotypes, as well as to the

promenivši svoje fenotipske i genotipske karakteristike, menjaju i metu delovanja antibiotika, i razvijaju visoku toleranciju na njih [34]. Biocidi promovišu toleranciju i smanjuju senzitivnost na antibiotike, razvijaju ukrštenu rezistenciju i korezistenciju kod patogenih bakterija [35].

Pandemija je uticala na nadzor, prevenciju i kontrolu antimikrobne rezistencije. Ograničena je mogućnost rada sa ustanovama koje kontrolišu antimikrobnu rezistenciju. Fondovi, ljudski i medicinski resursi (medicinsko osoblje, sanitarno osoblje, administrativno osoblje, zaštitna oprema, lekovi, reagensi za mikrobiološka ispitivanja) usmereni su na zbrinjavanje obolelih od KOVID-19 oboljenja [36].

Bakterije kao što su *Staphylococcus aureus*, *MRSA*, *Streptococcus pneumoniae* i *Streptococcus pneumoniae* rezistentan na penicilin, izolovane su u manjem broju tokom pandemije. Smatra se da su za ovo odgovorni: pojačana upotreba sredstava za dezinfekciju i pranje ruku, smanjenje socijalnih kontakata, nošenje maski, kao i povremeno zatvaranje školskih ustanova [37,38]. Sa druge strane, bakterije kao što su *Escherichia coli* i *Klebsiella pneumoniae* (posebno *Escherichia coli* rezistentna na treću generaciju cefalosporina kao i *Klebsiella pneumoniae* rezistentna na treću generaciju cefalosporina) izolovane su u većem broju, i takođe su imale proširen spektar antibiotske rezistencije tokom pandemije [37].

Tokom pandemije u 2020. godini u Srbiji, najčešće su izolovane bakterije iz uzoraka krvi bile: *Acinetobacter spp*. (28,3%), *Staphylococcus aureus* (15,5%), *Klebsiella pneumoniae* (15,4%), *Enterococcus faecalis* (12,4%), *Escherichia coli* (11,3%) i *Enterococcus faecium* (10,9%). Do značajnog porasta rezistentnih sojeva u 2020. godini je došlo kod *Pseudomonas aeruginosa* (za ceftazidim sa 59,0% do 64,0%, za ciprofloksacin sa 59,0% na 70,0%, za meropenem sa 55,0% na 62%). Takođe, *Staphylococcus aureus* je pokazao skok u broju izolovanih sojeva u 2020. godini, u odnosu na 2019. godinu (za ciprofloksacin sa 21,0% na 34,0% i za rifampicin sa 12,0% na 18,0%). Podaci su prikazani na osnovu još neobjavljenih rezultata ispitivanja sprovedenog u Laboratoriji Instituta za mikrobiologiju i imunologiju Medicinskog fakulteta Univerziteta u Beogradu.

ZAKLJUČAK

Uticaj KOVID-19 infekcije na globalnu antimikrobnu rezistenciju je još uvek nepoznat i verovatno će biti neravnomerno raspoređen u opštoj populaciji. Nesrazmerno velika upotreba antibiotika kod pacijenata sa KOVID-19 oboljenjem potencijalno može znatno pogoršati trenutno stanje, posebno u zemljama gde već postoji značajno visoka antimikrobna rezistencija. Oblasti u

development of the resistance to certain antimicrobial agents [33]. By changing their phenotypic and genotypic characteristics, these microbial subpopulations also change the target of antibiotic action and become highly tolerant to them [34]. Biocides promote tolerance and reduce antibiotic sensitivity, developing cross-resistance and co-resistance in pathogenic bacteria [35].

The pandemic has affected the monitoring, prevention and control of antimicrobial resistance. Cooperation with institutions that control antimicrobial resistance has been limited; funds, human and medical resources (medical staff, sanitation staff, administrative staff, protective equipment, drugs, reagents for microbiological tests) have been reallocated for treatment of COVID-19 patients [36].

Bacteria such as *Staphylococcus aureus*, MRSA, *Streptococcus pneumoniae*, and penicillin-resistant *Streptococcus pneumoniae* have been isolated in smaller numbers during the pandemic. It is believed that the increased use of disinfectants, hand washing, the limitation of social contacts, wearing face masks, as well as the occasional closing of schools are responsible for this [37,38]. On the other hand, bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* (especially *Escherichia coli* and *Klebsiella pneumoniae* resistant to 3rd generation cephalosporins) have been isolated in greater percentages and have also demonstrated an extended spectrum of antibiotic resistance during the pandemic [37].

In Serbia, during the pandemic in 2020, the most frequently isolated bacteria from blood samples were the following: *Acinetobacter spp*. (28.3%), *Staphylococcus aureus* (15.5%), *Klebsiella pneumoniae* (15.4%), *Enterococcus faecalis* (12.4 %), *Escherichia coli* (11.3%), and *Enterococcus faecium* (10.9%). There was a significant increase in the number of *Pseudomonas aeruginosa* resistant strains in 2020 (for ceftazidime from 59.0% to 64.0%, for ciprofloxacin from 59.0% to 70.0%, for meropenem from 55.0% to 62.0%). Also, *Staphylococcus aureus* showed an increase in the number of resistant strains in 2020, as compared to 2019 (for ciprofloxacin from 21.0% to 34.0%, and for rifampicin from 12.0% to 18.0%). The data are based on the study results conducted in the Laboratory of the Institute of Microbiology and Immunology of the Medical Faculty of the University of Belgrade.

CONCLUSION

The effect of COVID-19 on global antimicrobial resistance remains unknown and is likely to be distributed unevenly in the general population. The disproportionate use of antibiotics in patients with COVID-19 can significantly influence the current situation, especially in countries where significantly high antimicrobial resistance already exists. The areas where activities

kojima treba pojačati aktivnosti su edukacija stanovništva i lekara, praćenje vodiča dobre kliničke prakse od strane lekara, sprečavanje prepisivanja antibiotika u slučaju virusnih infekcija, ali i praćenje antimikrobne rezistencije od strane nadležnih mikrobioloških laboratorija, te razvijanje strategije za njeno sprečavanje.

Sukob interesa: Nije prijavljen.

should be intensified are the following: education of the population and medical staff, monitoring of the application of clinical practice guides and the use of antibiotics in viral infections, monitoring of antimicrobial resistance by competent microbiological laboratories, and development of strategies for its prevention.

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