JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Use of antibiotics in COVID-19 ICU patients

Lirim Mustafa[1], Ilir Tolaj[2], Nehat Baftiu[3,4], Hajrullah Fejza[5]

[1] *Department of Pharmacology, Faculty of Dental Medicine, University of Zagreb, Zagreb, Croatia*
[2] *Department of Infectious Diseases, Faculty of Medicine, University of Pristina, Pristina, Kosovo*
[3] *Department of Anesthesiology, Faculty of Medicine, University of Pristina, Pristina, Kosovo*
[4] *ICU, University Hospital Pristina, Pristina, Kosovo*
[5] *University for Busines and Technology, Pristina, Kosovo*

Abstract

Introduction: The role of antibiotics in the treatment in COVID-19 cases has not yet been adequately defined, and no criteria have been established for antibiotic treatment, type and duration.

Methodology: This paper reports the results of an observational study on the extent of antibiotic use in 52 randomly selected patients in the intensive care unit (ICU) at the University Hospital in Pristina, Kosovo with severe forms of COVID-19.

Results: Antibiotics were prescribed in all the cases (52; 100%). Of the 52 patients, 1) 13 (25%) were given antibiotics before hospitalisation, 2) 49 (94.2%) during treatment in the ward and 3) 52 (100%) during treatment in the ICU. Most often, empirical antibiotics were administered in 32 cases (61.5%) to treat methicillin resistant *Staphylococcus aureus* (MRSA) infections, and in 23 patients (44.2%) to treat atypical pathogens. The most prescribed antibiotics were ceftriaxone/cefotaxime plus macrolide in (17 cases; 32.7%), ceftriaxone/cefotaxime in (15 cases; 28.8%), ampicillin/amoxicillin plus clavulanic acid or sulbactam (five cases; 9.6%), and quinolones (five cases; 9.6%). Imipenem was the most frequently used antibiotic in the ICU (30 cases; 57.7%), followed by ceftriaxone (28 cases; 53.8%), and piperacillin/tazobactam and fluoroquinolone (17 cases; 32.7%). In 18 cases (34.6%), three antibiotics were given simultaneously; two antibiotics in 29 cases (55.8%) and in five cases (9.6%) only one antibiotic was given. The mean duration of antibiotic treatment was 12.71 days (3-22 days; SD 4.026).

Conclusions: The study showed unrestricted use of broad-spectrum antibiotics in the treatment of severe cases with COVID-19.

Key words: COVID-19; Antibiotics; ICU cases.

J Infect Dev Ctries 2021; 15(4):501-505. doi:10.3855/jidc.14404

(Received 24 November 2020 – Accepted 05 February 2021)

Introduction

Across the European Union/European Economic Area (EU/EEA) and the United Kingdom (UK), there has been a substantial increase in COVID-19 infections, representing a significant threat to public health. In most countries, infection rates have increased, with extreme levels in some areas [1]. The COVID-19 epidemic has changed the global focus of healthcare. In 80% of diagnosed cases, the symptoms are mild to moderate. Approximately 20% of patients are severely ill, and the disease is critical in 6% of affected patients [2]. For COVID-19 patients admitted to ICUs, the disease can be complicated by acute respiratory disease syndrome (ARDS), sepsis/septic shock and multiple organ failure [3]. The precise incidence of bacterial superinfection in COVID-19 patients is unknown but appears to be much lower than in severe influenza cases [4-6]. Most studies report initial co-infection or secondary bacterial pneumonia (11-35% of cases) in hospitalised patients caused primarily by *Streptococcus pneumoniae* and *Staphylococcus aureus* [5]. Notably, co-infection rates increased in critically ill patients admitted to the ICU globally [7]. Furthermore, there are no studies that have specifically investigated the development of superinfection by antimicrobial-resistant microorganisms in COVID-19 patients [8]. Studies worldwide of COVID-19 patients admitted to hospitals show that a high per cent (up to 94%) were prescribed antibiotics [9]. However, confirmed laboratory bacterial co-infections were low, from 3-14%, depending on whether the COVID-19 cases were treated in regular wards or the ICU [10,11]. The rationale for antibiotic treatment in COVID-19 patients appears to be based on experience with bacterial superinfection in influenza. In Kosovo, more than 60,000 COVID-19 cases have been registered to date, although the number of tests for SARS-CoV-2 has been limited. Of those, over 1,500 patients have died.

Kosovo has a population of about 1.5 million. The prescription of antibiotics in the treatment of COVID-19 cases in Kosovo is uniform, while their variety is unusual.

Methodology

This study was analytical and observational. It aimed to show the extent of antibiotic use in patients with severe forms of COVID-19 hospitalised in the ICU at the University Hospital in Pristina, Kosovo. The study evaluated the criteria on which physicians based their prescription of antibiotics, determined the duration of treatment, and evaluated the role of antibiotic use in the disease outcome. A total of 52 patients hospitalised in the ICU for COVID-19 were randomly selected from patient medical records. A confirmed case was defined by a positive result on a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a specimen collected with a nasopharyngeal swab. Data on antibiotic use were collected according to a modified Infectious Diseases International Research Initiative (ID-IRI) survey questionnaire. IBM SPSS Statistics Version 25 was used for statistical analysis; frequency tests were performed, analysing mean, minimum, maximum and standard deviation (SD) values.

Table 1. Primary characteristics, comorbidities, biological data, microbiological investigations and outcome of 52 ICU COVID-19 patients.

ICU patients with COVID-19	**N = 52**
Age, years [min-max]	61 (20–86)
Male, *n* (%)	35 (67)
Primary comorbidities	**n (%)**
Obesity (body mass index ≥ 30 kg/m^2)	23 (44)
Hypertension	9 (17)
Diabetes mellitus	21 (40)
Cardio-vascular diseases	8 (15)
Atrial fibrillation	10 (19)
Cerebro-vascular diseases	8 (15)
Venous thromboembolism	8 (15)
Chronic respiratory diseases	17 (33)
Chronic renal failure	14 (27)
Cerebro-vascular diseases	8 (15)
Patients with Comorbidities	**n (%)**
≥ 5 Comorbidities	8 (15)
4 Comorbidities	14 (27)
3 Comorbidities	12 (23)
2 Comorbidities	12 (23)
1 Comorbidity	6 (12)
Patient conditions before ICU admission	**n (%)**
Antibiotic therapy before (> 12 h) ICU admission	48 (92)
Days between the first symptom and ICU admission	9.3 (0–21)
Days between hospitalization and ICU admission	6.6 (2–12)
Biological data influencing antibiotic treatment at ICU admission	**N (%)**
Leukocyte's count	51 (98)
C-reactive protein	52 (100)
Procalcitonin	25 (48)
Outcomes in the ICU	**N (%)**
Invasive mechanical ventilation	38 (73)
CPAP	14 (27)
Renal replacement therapy	8 (15)
ICU mortality	29 (55.7)

Results

Of the 52 patients included in the study, 35 (67.3%) were male, and 17 (32.7%) were female. The average age was 61 years (min 20 - max 86, SD 15.47). All 52 patients had comorbidities, most with more than one. Of the 52 patients, 14 (26.9%) had four comorbidities, 12 (23.1%) had three, 12 (23.1%) had two, four (7.7%) had six, six (11.5%) had one, two (3.8%) had five, one (1.9%) had seven, and one (1.9%) had nine comorbidities. The most common comorbid condition was obesity (BMI≥30kg/m^2) in 23 cases (44.2%), followed by diabetes mellitus (21 cases; 40.4%), chronic respiratory diseases (17 cases; 32.7%), chronic kidney disease (14 cases; 26.9%), atrial fibrillation (10 cases; 19.2%), hypertension (9 cases; 17.3%), and cardiovascular, cerebrovascular, and thrombotic-embolic venous diseases (8 cases; 15.3%). Empirical treatment with antibiotics was prescribed in 48 cases (92.3%) before admission to the ICU. On average, 9.27 days (0 - 21 days, SD 2.85) elapsed from the disease's onset to ICU admission. The highest number of cases was admitted to the ICU 10 days after the onset of symptoms (17 patients; 32.7%). Fifteen patients (28.8%) were admitted on the 8th day, and 8 (15.4%) were admitted on the 7th day. Hospitalisation outside the ICU lasted an average of 6.63 days (2-12 days, SD 1.84), of which 14 patients (26.9%) were hospitalised for five days, 12 patients (23.1%) for seven days and 14 patients (26.9%) for eight days. All 52 patients admitted to the ICU had laboratory biological data on leukocytes, lymphocytes, and platelets, C-reactive protein (CRP) was available for 50 patients (96.2%), procalcitonin (PCT) was available for 14 patients (27%), and fibrinogen was available for seven patients (13.5%). All patients tested positive for SARS-CoV-2 RT-PCR. No microbiological tests for the presence of bacterial co-infection or superinfection were performed. All patients underwent radiological examinations of the lungs and had lung (chest) X-rays. Six patients (11.5%) underwent CT/MRI imaging of the lungs. The reason for admitting COVID-19 cases for treatment to the ICU was the severity of the disease. In 41 patients (78.8%),

the severity of the disease (severe clinical presentation) was the only reason for admission to the ICU. Six patients (11.5%) exhibited high inflammation markers, and five others (9.6%) showed radiological changes in their lungs. The treatment of cases in the ICU was complex. All patients were placed on oxygen therapy; 14 (26.9%) of them were on continuous positive airway pressure therapy (CPAP) and 29 patients (55.8%) were on mechanical ventilation. All patients were treated with antibiotics. All patients placed on mechanical ventilation died. Laboratory markers for inflammation were the primary reason for antibiotic treatment of all 52 patients. This treatment was followed by patient clinical evolution (11 cases; 21.1%) and pulmonary radiological findings (5 cases; 9.6%). Based on the inflammation markers, CRP was used in all of the patients, leukocytes were used in 51 cases (98.1%), and procalcitonin was used in 25 cases (48.1%). The primary data for the 52 ICU COVID-19 cases are presented in Table 1. Antibiotics were given to 13 patients (25%) before hospitalisation, 49 patients (94.2%) in the ward, and all patients in the ICU. ICU medical staff followed protocols for the use of antibiotics in almost all the cases (50 patients 96.2%). Empirical antibiotics were used to treat MRSA infections in 32 cases (61.5%), atypical pathogens in 23 cases (44.2%), and both treatments in four patients (7.7%). Fungi were not considered critical pathogens to be covered empirically.

The antibiotics used to treat patients in the ward, before admission to the ICU, included ceftriaxone/cefotaxime plus macrolide (17 cases; 32.7%), ceftriaxone/cefotaxime (15 cases; 28.8%), co-amoxiclav (6 cases; 11.5%), levofloxacin in (4 cases; 7.7%), co-amoxiclav plus macrolide (3 cases; 5.8%), co-amoxiclav plus fluoroquinolone (3 cases; 5.8%), and another antibiotic (not specified) in one case (1.9%). In the ICU, imipenem was the most frequently used (30 cases; 57.7%), followed by ceftriaxone (28 cases; 53.8%), fluoroquinolone (22 cases; 42.3%), piperacillin/tazobactam (17 cases; 32.7%), ceftazidime (3 cases; 5.7%) and meropenem (1 case; 1.9%). Three antibiotics were given simultaneously to 18 patients (34.6%), two antibiotics were given to 29 patients (55.8%), while five patients (9.6%) received only one antibiotic during treatment. The mean duration of antibiotic treatment for the ICU patients was 12.71 days (3-22 days, SD 4.026). Data on antibiotic use are summarised in Table 2.

Discussion

As in similar studies of COVID-19, there were more males than females (ratio 2:1), the mean age of the patients was 61 years (min 20, max 86, SD 15,475). All of the patients suffered from various underlying diseases, most with more than one accompanying illness. Obesity, diabetes mellitus, chronic respiratory diseases, and chronic kidney disease were the most common comorbidities. Various studies of patients with COVID-19 admitted to an ICU showed similar data on comorbidities [10,12-14]. COVID-19 symptoms started an average of 9.27 days (0-21, SD 2.857) before patients were admitted to the ICU; most were admitted on days 7, 8 and 10 after the onset of symptoms. Those patients were hospitalised for an average of 6.53 days (2-12, SD 1.847) before admission to the ICU; most cases were admitted on days 5, 7 and 8 of hospitalisation. Contou et al. [7] and Sharifipour et al. [13] demonstrated shorter periods for both scenarios. The study showed that the use of broad-spectrum antibiotics in patients with severe COVID-19 was universal. The data on the use of antibiotics for patients before hospitalisation, compared to those hospitalised, showed an extraordinary increase to 100% after

Table 2. Data on antibiotic use.

ICU patients with COVID-19	**N = 52**
Place when antibiotic prescribes	**N (%)**
Before hospitalization	13 (25)
In the ward	48 (92)
In the ICU	52 (100)
Aim of empiric use of antibiotics	**N (%)**
MRSA	32 (62)
Atypical pathogens	23 (44)
Other	4 (8)
Antibiotic used	**N (%)**
In the ward	
Ceftriaxone/cefotaxime plus macrolide	17 (33)
Ceftriaxone/cefotaxime	15 (29)
Co-amoxiclav	6 (12)
Levofloxacin	4 (8)
Co-amoxiclav plus macrolide	3 (6)
Co-amoxiclav plus quinolone	3 (6)
Anti-pseudomonal beta lactam	1 (2)
In the ICU	
Imipenem	30 (58)
Ceftriaxone	28 (54)
Fluoroquinolones	22 (42)
Piperacillin/tazobactam	17 (33)
Ceftazidime	3 (6)
Meropenem	1 (2)
Antibiotics/patient	**N (%)**
3 antibiotics	18 (34)
2 antibiotics	29 (56)
1 antibiotic	5 (10)

admission to the ICU. Before hospitalisation, only 25% of cases were treated with antibiotics, although the data may not be credible. During hospitalisation, antibiotics were prescribed in over 90% of the cases; in the ICU, they were prescribed for all patients. The use of antibiotics at this level was also reported by Miranda *et al.* [3]. While the primary reason for admitting cases to the ICU was the severity of the disease, the decision to use antibiotics relied more on laboratory markers of inflammation than on the clinical presentation of COVID-19. This finding can also be understood when considering that all patients admitted to the ICU had been seriously ill; and the gravity of the disease was considered a basic reason for antibiotic treatment, among other reasons. In the ID-IRI survey, the decision to use antibiotics was influenced primarily by the patient clinical presentation and, to a lesser extent, the laboratory markers of inflammation [2]. Among the laboratory markers of inflammation, CRP is considered an important factor depending on which antibiotics are prescribed. At the same time, PCT is used for this purpose in only about half the cases. PCT is considered the most important marker of inflammation influencing the decision to use antibiotics in a patient. However, one study concluded that CRP and PCT markers could appear in patients with COVID-19 without corresponding bacterial co-infection [6]. The causative flora of bacterial superinfections in COVID-19 remained unknown in our study (no sample was taken for microbiological research). However, in other studies, the overall proportion of COVID-19 patients with bacterial infections was 6.9% (95% CI 4.3-9.5%) [9]. In our research, the empirical use of antibiotics before admission to the ICU was more frequent (92.3%) than other studies [9,11]. Empirical administration of antibiotics is based on previous experience with bacterial superinfections in influenza or even community acquired pneumonia (CAP) treatment protocols. In recognition of these findings, coverage of MRSA and atypical pathogens has been the primary goal in selecting antibiotics for the treatment of these cases, before and after hospitalisation. Most participants in the study by Beović *et al.* [2] agree that atypical pathogens and staphylococci coverage is necessary, but without mentioning whether MRSA should be included. Further, coverage of atypical pathogens with macrolides and quinolones was not supported by Huttner *et al.* [5] and the COALITION II trial found no clinical benefits from the use of azithromycin in patients with COVID-19 [15]. In our study, ceftriaxone/cefotaxime plus macrolide was the most common combination given to patients before ICU admission (17 cases; 32.7%), followed by ceftriaxone/cefotaxime alone (15 patients; 28.8%), and ampicillin/amoxiclav plus clavulanic acid/sulbactam and quinolones (five cases each at 9.6%). This study also noted, same as the study of Alonso-Abelenda *et al.* [8], the biphasic use of antibiotics in COVID-19 cases, with the first wave of empirical antibiotic therapy and a second biphasic pattern with higher use of broad-spectrum antibiotics. In this study, imipenem was the most used antibiotic in the ICU in this study (30 cases; 57.7%), followed by ceftriaxone (28 patients; 53.8%), piperacillin/tazobactam (17 patients; 32.7%), in addition to fluoroquinolone or macrolides (35 patients; 67.3%). The same was reported by Beović *et al.* [2], while other studies mention diverse selections and combinations of antibiotics in cases with COVID-19. Based on the ID-IRI study (A) data, Pristina UCC physicians have combined practices from Europe and the USA. Most patients in the ICU were treated with a combination of antibiotics; three antibiotics (29 patients; 55.8%), two antibiotics (18 patients; 34.6%), and rarely with one antibiotic (5 patients; 9.6%). Miranda *et al.* [3] reported that, in COVID-19 cases, antibiotics are given in only 71% of cases; of these, 45% were part of combination therapy, and 25% were a single antibiotic. The similar high percentage (71.9%) of antibiotic administration in COVID-19 patients was also reported by Langford *et al.* [9]. In our study, the duration of antibiotic treatments in the ICU was longer (12.71 days, SD 4.026) than reported in other studies [2], in which antibiotic treatment lasted 5-8 days. This finding indicates the non-critical use of antibiotics in most of the COVID-19 cases, which practice has been opposed by European Study Group on Antibiotic Policies (ESGAP) [5].

The role and possible benefit of antibiotic use in the ICU disease outcomes could not be established. The universal use of antibiotics in all cases included in the study made this impossible. The general and excessive use of antibiotics in COVID-19 patients, as our study shows, rises concerns about antibiotic over-prescribing, including resistance, various adverse effects, and the economic burden on patients and health institutions. This trend emphasises the importance of antibiotic stewardship in treatment decision-making.

Conclusions

Addressing severe clinical cases of COVID-19 in light of ineffective etiological treatment will challenge doctors who treat those cases. Non-critical use of antibiotics in COVID-19 cases is a consequence of limited treatment options. In countries with inadequate

healthcare systems, the indiscriminate use of antibiotics, even before COVID-19 pandemics, was normal. This practice can lead to increased antibiotic resistance, making it more challenging to treat patients with severe infections. Under current conditions with the ongoing COVID-19 pandemic, the concept of antibiotic stewardship is even more essential.

Institutional Review Board Statement

Ethical review and approval were waived for this study. According to the National Code on Clinical trials, this is a proper observational retrospective study for which ethical approval is not required.

Informed Consent Statement

Patient consent was waived due to the study's retrospective nature; all procedures performed were part of routine care.

Author's contributions

LM concived the original idea. IT designed, supervised and provided a critical reading of the manuscript. NB, LM and HF made data analyses. All the authors made the final approval of the article for publication.

References

1. European Centre for Disease Prevention and Control. Rapid Risk Assessment: Increased transmission of COVID-19 in the EU/EEA and the UK-thirteen update (2020) Available: https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-increased-transmission-thirteenth-update. Accessed 23 October 2020.
2. Beovic B, Dousak M, Ferreira-Coimbra J, Nadrah K, Rubulotta F, Belliato M, Berger-Estilita J, Ayoade F, Rello J, Erdem H (2020) Antibiotic use in patients with COVID-19 (2020) a 'snapshot' Infectious Diseases International Research Initiative (ID-IRI) survey. J Antimicrob Chemother 75: 3386-3390.
3. Miranda C, Silva V, Capita R, Alonso-Calleja C, Igrejas G, Poeta P (2020) Implications of antibiotics use during the COVID-19 pandemic: present and future. J Antimicrob Chemother 75: 3413-3416.
4. Fattorini L, Creti R, Palma C, Pantosti A (2020) Bacterial co-infections in COVID-19: an underestimated adversary. Ann Ist Super Sanita 56: 359-364.
5. Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J (2020) COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect 26: 808-810.
6. Lansbury L, Lim B, Baskaran V, Lim WSh (2020) Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect 81: 266-275.
7. Contou D, Caludinon A, Pajot O, Micaëlo M, Flandre PL, Dubert M, Cally R, Logre E, Fraisé M, Mentec H, Plantaféve G (2020) Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care 10: 119.
8. Abelanda-Alonso G, Padullés A, Rombauts A, Gudiol C, Pujol M, Alvarez-Pouso C, Jodar R, Carratalá J (2020) Antibiotic prescription during the COVID-19 pandemic: A biphasic pattern. Infect Control Hosp Epidemiol 41: 1371-1372.
9. Langford JB, So M, Raybardhan S, Leug V, Westwood D, MacFadden DR, Soucy JR, Daneman N (2020) Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect 26: 1622-1629.
10. Neto GM, Lo KB, Salacup G, Pelayo J, DeJoulll R, Bhargav R, Gul F, Peterson E, Albano J, Patarroyo-Aponte G, Rangaswami J, Azmaiparashvili Z (2020) Bacterial infections and patterns of antibiotic use in patients with COVID-19. J Med Virol 93: 1489-1495.
11. Vaugh VM, Gandhi T, Petty LA, Patel PK, Prescott HC, Malani AN, Ratz D, McLaughlin E, Chopra V, Flanders SA (2020) Empiric Antibacterial Therapy and Community-onset Bacterial Co-infection in Patients Hospitalised with COVID-19: A Multi-Hospital Cohort Study. Clin Infect Dis ciaa1239.
12. Richardson S, Hirsch JS, Narasimhan N, Crawford JM, McGinn TH, Davidson KW (2020) Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalised With COVID-19 in the New York City Area. JAMA 323: 2052-2059.
13. Sharifipour E, Shams S, Esmkhani M, Khodadai J, Fotouhi-Ardakani R, Koohpaei A, Doosti Z, Golzari SAJ (2020) Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. BMC Infect Dis 20: 646.
14. Instituto Superiore di Sanita. Characteristics of Covid-19 patients dying in Italy-Report based on available data on April 9th. Available: https://www.epicentro.iss.it/en/coronavirus/bolletino/Report-COVID-2019_9_april_2020. Accessed 9 April 2020.
15. Oldenburg CE, Doan Th (2020) Azithromycin for severe COVID-19. Lancet 396: 956-937.

Corresponding author

Ilir Tolaj, MD, PhD, Infectious Diseases Specialist, Head of the Department
Department of Infectious Diseases, Medical Faculty, University of Pristina
Bulevard of Martirs nn, 10000 Pristina, Kosovo
Phone: +383 49 888 298
Email: ilir.tolaj@uni-pr.edu, drtolaj@gmail.com

Conflict of interests: No conflict of interests is declared.