Prevalence of Antibiotic Use in Hospitalized COVID-19 Patients: An Observational Study in Secondary Healthcare Hospitals in Kosovo

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ABSTRACT

INTRODUCTION: Globally, the high use of antibiotics among hospitalized patients diagnosed with COVID-19 has been reported despite evidence that bacterial coinfections are uncommon. This issue raised our concerns, as there was a report on high frequency of antibiotic resistant bacterial infections in COVID-19 patients admitted to the intensive care unit. Thus, we conducted a study to determine the prevalence of antibiotic use for hospitalized acute COVID-19 infection in secondary healthcare hospitals in Kosovo. **MATERIALS AND METHODS:** A cross sectional study was conducted among patients with acute COVID-19 admitted to secondary healthcare hospitals in Kosovo. A modified Infectious Diseases International Research Initiative (ID-IRI) questionnaire was used to collect information in 460 COVID-19 PCR positive patients. **RESULTS:** All studied patients (100%) were treated with antibiotics. An empirical antibiotics were used to cover Methicillin-*resistant Staphylococcus aureus (MRSA)* infections in 136 cases (29.6%), methicillin-susceptible Staphylococcus aureus (MSSA) infections in 86 cases (18.7%), atypical pathogen in 174 cases (37.8%), and Pseudomonas infections in 48 cases (10.4%). The most frequently used antibiotics were ceftriaxone/cefotaxime plus macrolide (149 cases; 31%), ceftriaxone/cefotaxime plus quinolone (85 cases; 17.7%), and co-amoxiclav plus fluoroquinolone (78 cases; 16.3%). Imipenem was most frequently used in the ICU (64 cases; 13.3%). **CONCLUSION:** Despite the antibiotic guidelines clearly stated that antibiotics should only be used in confirmed case of secondary bacterial infections including the COVID-19 patients, our study revealed that the overused of antibiotics remained unchanged. As the misused and overused of antibacterial has been shown to accelerate the emergence and spread of antibacterial resistant, the inappropriate practice should be changed.

INTRODUCTION

Despite the lack of verification regarding antibiotics effect on SARS-CoV2 and the minor presence of bacterial infections, antibiotics have been broadly used in the treatment of patients with COVID-19 during the pandemic.[1] The prevalence of bacterial community-acquired co-infection and secondary infection in COVID-19 hospitalized patients were low (3.1-3.5% and 4.7-14.3% respectively).[2,3] *Streptococcus pneumoniae* and *Staphylococcus aureus* are the main causative agents of community-acquired co-infections whereas *Pseudomonas aeruginosa* and *Escherichia coli* are the main causes of bacterial superinfections.[2] A meta-analysis shown that the prescribing rate of antibiotics in COVID-19 patients was remarkably high (74.6%) whereas the estimated bacterial co-infection was only 8.6%, reflecting the unnecessary antibiotic use in COVID-19 patients.[3] A literature review revealed that the major use of antibiotics amongst Covid-19 hospitalized patients was mainly in an empirical setting with no proven efficacy of the practice.[4] A scoping review shown a better outcome in COVID-19 patients who were prescribed clinically justified antibiotics than those who were not clinically justified, demonstrated by lower

mortality rates (9.5% vs. 13.1%), higher discharge rates (80.9% vs. 69.3%), and shorter length of hospital stay (9.3 days vs. 12.2 days).[5] A retrospective study reported that cephalosporins, macrolides, quinolones, and ampicillin/clavulanic acid were the most prescribed antibiotics among hospitalized COVID-19 patients.[6-10] A study showed the pattern of antibiotic use in patients with COVID-19 and bacterial infections, highlighting the urgent need for further research to assess the effect of COVID-19 on antimicrobial resistance at both the patient and population levels.[10] Thus, we conducted a study aimed to describe the prevalence of antibiotic use in hospitalized COVID-19 patients in hospitalized patients in secondary healthcare hospitals in Kosovo.

MATERIALS AND METHODS

This was a cross-sectional, observational clinical study conducted to determine the prevalence of antibiotic use among acute COVID-19 patients admitted to secondary healthcare hospitals in Kosovo. A total of 460 COVID-19 positive patients diagnosed by PCR were included in the study. A modified Infectious Diseases International Research Initiative (ID-IRI) survey questionnaire was used for primary data collection. IBM SPSS Statistics Version 25 was used for statistical analyses in which the descriptive and categorical variables were reported as frequencies and percentages.

RESULTS

Out of 460 PCR positive COVID-19 patients admitted to secondary healthcare hospitals in Kosovo, majority of them were male (298 cases, 64.8%) and of advanced age (mean 61 years old) with age ranges from 2 years old to 91 years old. Majority of the patients had comorbidities (438 cases, 91.5%) with more than half of them had two or more comorbidities (290 cases, 60.4%). The most frequently identified comorbidities were diabetes mellitus, hypertension and cardiovascular diseases (262 patients, 56.9%; 235 patients, 50.4%; and 188 patients, 40.8% respectively). Other comorbid conditions in our studied patients includes obesity, chronic respiratory diseases, chronic renal diseases, and malignant diseases.

Majority of our studied patients were initially admitted into the general ward (368 patients, 80%), and only 20% (92 patients) were admitted directly into the ICU. The initial symptoms of COVID-19 were started 6 days (2-8 days) prior to the hospital admission. The average time from admission to the hospital to the need for transfer to the ICU or university hospital due to deterioration of the condition was 7 days (1-12 days). The length of hospitalization was 12.71 days (3-22 days). All studied patients had Complete Blood Count (CBC) results, 432 patients (93.9%) had C-reactive protein (CRP) results, and 152 patients (33%) had procalcitonin (PCT) results. All cases were positive for SARS-CoV-2 RT-PCR. No microbiological evaluation was done to detect eventual bacterial co-infection or superinfection.

All studied patients underwent chest X-rays, while only a few of them underwent computed tomography scan (CT scan) or magnetic resonance imaging (MRI) of the lungs. The indication for the COVID-19 patient's admission to the hospital was the severity of the disease and this was the only indication for ICU admission for most of the patients, (82 patients, 89%). The investigations result shown that 48 patients (10.4%) had an increased in inflammatory markers and 326 patients (70.9%) had changes on the lung x-rays. All patients were treated with oxygen therapy in which 128 patients (27.8%) were put on continuous positive airway pressure therapy (CPAP) and 57 patients (12.4%) on mechanical ventilation. Unfortunately, all COVID–19 patients placed on mechanical ventilation died. The data for the 460 COVID-19 patients are presented in Table 1.

All of our studied patients received antibiotic treatment as it was considered a standard protocol for the treatment of COVID-19 patients. The antibiotics prescriptions were not based on any specific inflammatory markers or radiological findings. The empirical antibiotics were prescribed to treat various types of bacterial infections including 136 cases of Methicillin-resistant Staphylococcus aureus (MRSA) infection (29.6%), 86 cases of methicillin-susceptible Staphylococcus aureus (MSSA) infections (18.7%), 174 cases of atypical pathogen infections (37.8%) and 48 cases of Pseudomonas infections (10.4%). As the fungal infections were not considered a critical pathogen, it was

Table 1. Characteristics, comorbidities, biological data, and outcome of COVID-19 patients
n=460

Age, years [min-max]	61 (2-91)
Males, n (%)	298 (64.8)
Primary co-morbidities	**N (%)**
Obesity (body mass index ≥ 30 kg/m2)	102 (22.17)
Hypertension	232 (50.4)
Diabetes mellitus	262 (56.9)
Cardio-vascular diseases	188 (40.8)
Chronic respiratory diseases	152 (33)
Chronic renal diseases	78 (16.9)
Malignant diseases	36 (7.8)
Other	18 (3.9)
Patients with Co-morbidities	**N (%)**
≥ 5 co-morbidities	28 (6.1)
4 Co-morbidities	32 (6.9)
3 Co-morbidities	104 (22.6)
2 Co-morbidities	126 (27.4)
1 Co-morbidity	148 (32.2)
0 Co-morbidities	22 (4.8)
Data before admission (ward and ICU)	**N (%)**
Antibiotic therapy before (> 24 h) hospital admission	392 (81.7)
Days between the first symptoms and hospital admission	7 (0–21)
Days between hospitalization and ICU admission	7 (1–12)
Type of admission	**N (%)**
Hospital ward	368 (80)
ICU unit	92 (20)
Outcome	**N (%)**
Invasive mechanical ventilation	57 (12.4)
CPAP	128 (27.8)
Renal replacement therapy	8 (1.7)
Mortality	70 (15.3)
Transferred to university hospital	50 (10.9)

not treated empirically. The antibiotics used were a combination of macrolide with ceftriaxone/cefotaxime (149 cases, 31%), ceftriaxone/cefotaxime alone (65 cases, 13.5%), combination of quinolone with ceftriaxone/cefotaxime (85 cases, 17.7%), co-amoxiclav alone (10 cases, 2.1%), combination of macrolide with co-amoxiclav (36 cases, 7.5%) and combination of quinolone with co-amoxiclav (78 cases, 16.3%).

In the ICU setting, imipenem was most frequently used antibiotics (64 cases, 13.3%), followed by piperacillin/ tazobactam (36 cases, 7.5%) and meropenem (2 cases, 0.4%). In terms of antibiotics regimes, 4 patients received 4 antibiotics simultaneously (0.8%), 37 patients received 3 simultaneous antibiotics (7.7%), 334 patients received 2 simultaneous antibiotics (69.6%), and 68 patients were treated only with one antibiotic (14.2%). The mean duration of antibiotic treatment was 9.22 days (ranging from 3 to 22 days). Antibiotics were prescribed to 392

patients (81.7%) patients prior to their hospitalization. All studied patients received antibiotics during hospitalization. The antibiotics usage data are presented in Table 2.

Table 2. Data on antibiotic use - N = 460

Antibiotic/s prescribed	N (%)
Prior hospitalization	392 (81.7)
Hospitalized in ward	362 (100)
Hospitalized in the ICU	92 (100)
Aim of empirical antibiotic/s use	**N (%)**
MSSA	86 (18.7)
MRSA	136 (29.6)
Atypical pathogens	174 (37.8)
Pseudomonas aeruginosa	48 (10.4)
Other	34 (7.4)
In ward used antibiotic/s	**N (%)**
Ceftriaxone	65 (13.5)
Co-amoxiclav	10 (2.1)
Ceftriaxone plus macrolide	149 (31)
Co-amoxiclav plus macrolide	36 (7.5)
Ceftriaxone plus quinolone	85 (17.7)
Co-amoxiclav plus quinolone	78 (16.25)
ICU antibiotic/s use	**N (%)**
Imipenem	64 (13.3)
Piperacillin/tazobactam	36 (7.5)
Meropenem	2 (0.4)

DISCUSSION

Our study demonstrated the highly prevalence of broad-spectrum antibiotics prescription in severe COVID-19 patients. The data regarding the antibiotics administered in patients prior and after the hospitalization exhibited an exceptional rise to 100% after admission to the hospital. Although our data recorded that 31% of patients had received antibiotics prior to the hospital admission, the credibility of this data may be questionable. Antibiotics were prescribed in 100% of our hospitalized patients regardless whether the patients were admitted to the general ward or intensive care unit. The utilization and combination of antibiotics were empirical and only based on clinical judgment and fear of bacterial complications, with no microbiological analyses conducted to confirm or exclude the presence of bacterial infection during COVID-19 disease.

Similar studies on this issue produced varying results world widely. A review of a study conducted in two hospitals in London where shown similar results in which 98% of the patients received antibiotic treatment, even though the percentage of bacterial co-infections was low (2.7%),. Another similar study revealed that despite the low percentage of bacterial infections confirmed by blood

culture (4.2%), empirical antibiotic used was high (80%).[2] In Netherlands, even though only 1.2% of COVID-19 patients had a confirmed bacterial infection, 60.1% of them received antibiotic treatment before admission to the hospital.[2]

In another observational study conducted across multiple centers found that although the presence of nocturnal infections was only 6.3%, antibiotics were used in 59.8% of patients.[2]

A review of antibiotics in treatment of COVID-19 complications found that antibiotics were administered in 74.6% (95% CI 68.3-80.0%) of cases, while the prevalence of bacterial co-infections was only 8.6% (95% CI 4.7-15.2%). The review also reported that although the bacterial infections were present in only 17.6% of patients, the antibiotics were used in 74.0% of patients. The same review revealed that antibiotics were used in 75.4% of severely ill patients, and 75.1% of mild or moderately severe patients.[4]

However, the rate of prescribing antibiotics without clinical relevance was 51.5% in mild and moderately severe illness and 41.9% in severely ill patients.[5] A study by Albert Einstein Medical Center Philadelphia found that 67% of patients were treated with antibiotics even though 72% of them had no confirmed bacterial infections.[6] Our study's results are consistent with the aforementioned research, demonstrating a substantial use of empirical antibiotics prior to hospitalization. Nevertheless, the absence of microbiological investigations to identify bacterial infections in our study's patients suggests the inadequate operation of these services during the pandemic. The study's findings also indicate a potential lack of physician interest in identifying bacterial infections in patients with COVID-19.

In a meta-analysis published in JAMA, it was reported that although antibiotics were given to 37% of patients in the UK prior to the hospitalization and 85% of patients during hospitalization in which one or more antibiotics being used simultaneously, only 2.4% of these patients had bacterial infections.[11] A study conducted in Spain found that the antibiotics prescription in the studied patients were appropriately prescribed (43.9%), inappropriately prescribed (34.2%), and not prescribed (21.6%).[12] A Turkish study shown that 74.5% of patients were treated with antibiotics in which 37.2% of them were treated with a combination of antibiotics, although 71.2% of them had neither clinical diagnosis nor microbiological data to justify their use.[7]

A study conducted in Indonesia shown that even though bacterial cultures were positive in 18.3% of patients, 83.4% of them were treated with antibiotics in which azithromycin were prescribed in 44.3% of patients.[13] Daria and Islam showed that in South Asia, antibiotics were widely used with 72% of patients receiving different antibiotics, although only 1-16% of cases had data on the presence of bacterial infections. Antibiotics were given to 100% of ICU patients. A study in conducted in Bangladesh revealed that the most frequently given antibiotics were third-generation cephalosporins (60%), followed by macrolides (40%). Another study conducted in Pakistan, revealed that t88.1% of COVID-19 cases were treated with multiple antibiotics without any microbiological or other tests and azithromycin being the most frequently given antibiotic. Another similar study conducted in India revealed a significant increase in the sale of antibiotics during the COVID-19 pandemic.[8]

A study conducted in Nepal demonstrated that antibiotics were prescribed in 98.11% of cases, with more than one antibiotic being given in 71.15% of them, with ceephalosporins were the most frequently reported (81.73%), followed by macrolides (54.81%).[14] In another study conducted in Bangladesh shown that 94.13% of the patients were prescribed antibiotics regardless of the severity of the disease.[15] In our study, the use of more than one antibiotic in patients with COVID-19 was very high in which 392 patients or 85.22% of them being treated with a combination of antibiotics selected empirically. As more developed countries with consolidated and advanced health systems are very strict in prescribing antibiotics for patients with COVID-19, a study conducted in Japan shown that antibiotic prescription is relatively low for acute COVID-19 in Japan. The study also shown that the antibiotic prescription was associated with older age, multi-

morbidity, severe disease, and winter season. The same study reported that the antibiotics were prescribed to 16.15% hospitalized COVID-19 patients with life-threatening and only 10.53%.for outpatients.[9]

A study conducted in Hong Kong, only 29.1% of cases were treated with antibiotics, although only 1.84% of them had confirmed bacterial infection, in which the most frequently prescribed antibiotics were amoxicillin + clavulanic acid, ceftriaxone, and doxycycline.[16] A study conducted in Malaysia showed that the use of antibiotics was 17.1% of cases, with two or more antibiotics being given in 5.5% of cases, with the most frequently given antibiotics were amoxicillin/clavulanic acid (37.8%), followed by ceftriaxone (12.3%), piperacillin/tazobactam (13.3%), azithromycin (8.3%), and meropenem (7.0%).[17] The commonest used groups of antibiotics among the patients with COVID-19 in our study as well as in other studies discussed were third-generation cephalosporins, macrolides, and fluoroquinolones.

From our study, we identified one important limitation in which in all the secondary health care hospitals included in the study, the antibiotic utilization was not analyzed to look for the differences between age groups, and there was no correlation between variables tested.

CONCLUSIONS

Despite the introduction of new treatment options and guidelines, the utilization of antibiotics in COVID-19 cases in our country remained unchanged during the pandemic. In countries with inadequate healthcare systems, the incorrect use of antibiotics persisted, posing a risk of escalating antibiotic resistance. Therefore, it is crucial to implement antibiotic stewardship principles in such situations, thus ensuring a more prudent use of antibiotics in COVID-19 patients to prevent the development of antibiotic-resistant bacteria.

CONFLICT OF INTEREST

All authors declare disclosure of all relationships that could be viewed as presenting a potential conflict of interest.

INSTITUTIONAL REVIEW

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.

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