Vol. 26 (2023) 21–30 DOI: https://dx.doi.org/10.4314/ecajps.v26i1.4

Antibiotic Prescribing Patterns among Patients Suffering from COVID-19 at a Tertiary Teaching and Referral Facility in Kenya: Findings and Implications

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The indiscriminate use of antibiotics during the coronavirus disease of 2019 (COVID-19) pandemic may fuel antimicrobial resistance. This study aimed to determine the antibiotic prescribing patterns among COVID-19 patients in a tertiary healthcare facility in Kenya. A retrospective cross-sectional study was conducted with data extracted from 138 patient medical records. Data was collected on severity of COVID-19 disease, laboratory tests, comorbidities, antibiotic use, and analyzed using Statistical Package for Social Sciences version 25 at $p \leq 0.05$. Antibiotic prescribing was at 67.4% with azithromycin (52.9%) and amoxicillin-clavulanate (47.1%) being the most common. Most patients (48.6%) received two antibiotics concomitantly, principally with azithromycin and co-amoxiclav (31.2%). Severity of COVID-19 ($p<0.0001$), presence of diabetes mellitus ($p=0.018$) and elevated procalcitonin ($p=0.008$) were significantly associated with antibiotic use. Clinicians used antibiotics based on the severity of COVID-19 and presence of comorbidity, which should be discouraged. Further research is needed to establish the long-term effects of antibiotic use in COVID-19 patients.

Keyword: COVID-19, severity, comorbidities, antibiotics prescribing patterns

INTRODUCTION

Antibiotics continue to play a critical role in modern medicine due to the large burden of infections globally. The misuse and overuse of antibiotics is rampant across the world and contribute significantly to emergence of antimicrobial resistance (AMR).[1] Furthermore, with the advent of the coronavirus disease of 2019 (COVID-19), appropriate use of antibiotics has proven to be a challenge, with the healthcare system trying to mitigate the effects of the pandemic.[2] Even healthcare centers with established antimicrobial stewardship programs have had their challenges exposed in relation to antibiotic use during the pandemic.[3]

Studies reveal a 36% increase in antibiotic prescriptions worldwide.[4] The rising over-prescription of antibiotics has fueled AMR.[5] According to a survey conducted to identify the trends of antibiotic prescribing in Cameroonian healthcare facilities, 37% of the 30,096 prescriptions examined contained an antibiotic.[6] Studies conducted in Kenya depict high prevalence of antibiotic prescribing, being 81.7% among inpatients and 72.9% in outpatients.[7]

There is currently relatively limited data on COVID-19 patients developing secondary bacterial infection. However, two studies found that less than 10% of patients had subsequent bacterial infections[8] whereas a meta-analysis reported that among critically ill patients, the extent of bacterial coinfection was 8%.[9] According to one study, there have been substantially high usage of antibiotics when treating COVID-19 patients, with up to 45% of patients being on antibiotic treatment despite relatively low confirmation rate of secondary bacterial infection.[8] This prescription practice stems from the rationale that the viral infection associated with COVID-19 causes immune suppression increasing the likelihood of bacterial co-infections.[10] Antibiotic use was therefore embraced as a potential strategy for mitigating the effects of the viral infection.[11]

Research on COVID-19 patients in a hospital in China showed that 71% of the patients received

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antibiotics in the course of their treatment.[12] A study conducted in Tygerberg Hospital, South Africa, reported that 258 of the 363 adult patients admitted to an intensive care unit (ICU) with severe COVID-19 pneumonia received early empirical antibiotics within the first 48 hours of admission. Amoxicillin-clavulanate (co-amoxiclav), azithromycin, and meropenem were predominantly used.[13] A review carried out in Kenyatta National Hospital (KNH) on commonly used drug therapies for COVID-19 patients revealed that co-amoxiclav, azithromycin, and ceftriaxone were the most commonly used antibiotics at 37%, 30%, and 5%, respectively.[14] Although the rampant use of antibiotics is reported across the world, the pattern of use during management of COVID-19 has not been extensively studied in Kenya. This study sought to determine the prevalence and factors influencing antibiotic prescribing at KNH. By examining demographic, clinical and laboratory characteristics of COVID-19 patients, we sought to elucidate the prescribing patterns in a resource-constrained setting.

METHODS

Study design

A retrospective cross-sectional study design was adopted. The study was conducted at KNH, a Level 6 hospital in Nairobi County. Medical records for patients admitted at the KNH Infectious Disease Unit (IDU) in the period spanning June 2020 to December 2021 were reviewed. Data was collected from patients in both the ICU and general wards.

Study population, inclusion and exclusion criteria

The study population comprised of COVID-19 patients in Kenya. The study targeted COVID-19 adult patients who received antibiotic therapy during their course of treatment at KNH. All adult patients (≥18 years) with a confirmed diagnosis of COVID-19 and admitted at the IDU in the period June 2020 to December 2021 were included in the sampling frame. Conversely, patients with chronic infections such as tuberculosis or those on long-term antibiotic use were excluded. Further, patients diagnosed with COVID-19 with incomplete medical records such as regarding treatment regimen were also excluded.

Sample size and sampling method

The main outcome variable in this study was the prevalence of antibiotic use in the treatment of COVID-19 patients. Previous studies had shown that the prevalence of antibiotic use in COVID-19 patients was approximately 72%.[15] The estimated sample size was 310 based on the formula postulated by Cochran (1977) for such epidemiological studies.[16] However, due to limited time and personnel, a reduction in the sample size was necessary. A reduction formula was used to determine the minimum sample size which was 125. Nonetheless, to account for data losses, a 10% contingency was added to make a sample of 138 medical records which were used for the study.

Sampling technique

Random sampling was applied to attain the sample size. To achieve this, medical records for COVID-19 patients were obtained and thereafter the ones that met the inclusion criteria were singled out. After checking whether they had the relevant information, the patient file numbers were entered into the Microsoft Excel version 2013 and the computer generated a random sample of 138 files to be studied.

Data collection

A semi-structured questionnaire was used to extract raw data from the medical files. The form was divided into three sections. The first section captured the patient's sociodemographic data including age, gender, occupation and county of residence. Based on World Health Organization (WHO) guidelines, patients were categorized into three groups namely mild, moderate, or severe COVID-19 disease.[17] The second section extracted information regarding the type of antibiotics prescribed, dose, frequency, route of administration, duration of treatment and whether the antibiotic was initiated on admission. The third section focused on biomarker levels, culture and sensitivity tests, imaging techniques, and presence of comorbidities.

Statistical analysis

The collected data was validated for completeness and accuracy by cross-checking

with the data extraction forms and keyed into Microsoft Excel version 2013. It was then transferred to IBM Statistical Package for Social Sciences (SPSS) version 25 for analysis. Descriptive analysis was done for the study population in terms of sociodemographic factors including age and gender, as well as clinical characteristics such as severity of disease. Bivariate analysis was used to establish the relationship between sociodemographic and clinical characteristics versus severity of disease or antibiotic prescribing patterns. A *p*-value of ≤0.05 was considered statistically significant.

Ethical approval

Ethical approval was obtained from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC) vide approval reference number UP124/02/2022. Further authorization was obtained from the KNH-IDU. Confidentiality of the data was strictly upheld throughout the study.

RESULTS`

Sociodemographic characteristics

The sociodemographic characteristics of the study participants are shown in Table 1. Majority of the participants were male (84, 60.9%) and the mean age of the study population was 48 (±14.4) years, with a range of 21-93 years. Approximately 23.9% of the participants were aged 40-49 years and patients 50 years and above accounted for majority at 45.7%.

Table 1: Patient sociodemographic characteristics

Variable	Frequency, n (%)	Variable	Frequency, n (%)
Gender		**Religion**	
Male	84 (60.9)	Christian	135 (97.8)
Female	54 (39.1)	Muslim	3 (2.2)
Age (years)		**History of smoking**	
18-29	12 (8.7)	Yes	2 (1.4)
30-39	30 (21.7)	No	54 (39.1)
40-49	33 (23.9)	Unknown	82 (59.4)
50-59	31 (22.5)	**Alcohol abuse**	
60-69	23 (16.7)	Yes	8 (5.8)
≥70	9 (6.5)	No	49 (35.5)
		Unknown	81 (58.7)
Marital status		**Comorbidities**	
Single	19 (13.8)	Diabetes	36 (59.0)
Married	115 (83.3)	Hypertension	35 (57.4)
Widowed	3 (2.2)	HIV	8 (13.1)
Separated	1 (0.7)	Asthma	4 (6.6)
Occupation		Obesity	4 (6.6)
Employed	40 (29.0)	Renal failure	3 (4.9)
Self-employed	81 (58.7)	Cancer	2 (3.3)
Retired	17 (12.3)	CHF	1 (1.6)

HIV= Human immunodeficiency virus; CHF= Congestive heart failure.

Severity of COVID-19

When stratified by the severity of their COVID-19 status as per the WHO guidelines[17], 49.3%, 28.3%, and 22.5% of participants exhibited moderate, mild, and severe COVID-19, respectively.

Prevalence of antibiotic prescribing and culture and sensitivity testing

Management of COVID-19 in 93(67.4%) patients involved at least one antibiotic (Table 2). Among these, 15 (10.9%) patients were treated using one antibiotic, while 67(48.6%), 7(5.1%), and 4(2.9%) patients received two, three and four antibiotics, respectively. On the other hand, culture and sensitivity testing was carried out in

only 7(5.1%) patients to assess for bacterial coinfection.

Specific antibiotic prescribed

Table 3 displays the types of antibiotics prescribed. Azithromycin was the most prescribed antibiotic (78.5%) followed by co-amoxiclav (69.9%). The most prescribed antibiotic combination was azithromycin and co-amoxiclav at 31.2%.

Table 2: Prevalence of prescribing antibiotics, and culture and sensitivity testing

Characteristic	Response	Frequency n (%)
Antibiotic prescribed	Yes	93 (67.4)
	No	45 (32.6)
Number of antibiotics prescribed	0	45 (32.6)
	1	15 (10.9)
	2	67 (48.6%)
	3	7 (5.1%)
	4	4 (2.9%)
Antibiotic initiated on admission	Yes	73 (52.9%)
	No	65 (47.1%)
Culture and sensitivity testing	Yes	7 (5.2%)
	No	131 (94.8%)

As shown in Figure 1, there was widespread use of oral azithromycin 500 mg for 3 days which was administered to 60 (64.5%) of the 93 patients put on antibiotic therapy. Intravenous co-amoxiclav 1.2 g for 5 days was prescribed to 36 (38.7%) patients, showing a high utilization rate.

Table 3: Specific antibiotic prescribed

Variable	n (%)
Antibiotic	
Azithromycin	73 (78.5)
Co-amoxiclav	65 (69.9)
Ceftriaxone	29 (31.2)
Cefuroxime	2 (2.2)
Clarithromycin	4 (4.3)
Ciprofloxacin	2 (2.2)
Metronidazole	5 (5.4)
Meropenem	3 (3.2)
Ceftazidime	1 (1.1)
Levofloxacin	1 (1.1)
Antibiotics used as monotherapy	
Co-amoxiclav	6 (6.5)
Azithromycin	5 (5.4)
Ceftriaxone	2 (2.2)
Cefuroxime	1 (1.1)
Levofloxacin	1 (1.1)
Antibiotic combinations	
Azithromycin + Co-amoxiclav	43 (46.2)
Azithromycin + Ceftriaxone	16 (17.2)
Co-amoxiclav + Clarithromycin	2 (2.2)
Co-amoxiclav + Metronidazole	1 (1.1)
Ceftriaxone + Metronidazole	2 (2.2)
Co-amoxiclav + Azithromycin + Ceftriaxone	4 (4.3)
Co-amoxiclav + Ceftriaxone + Clarithromycin	1 (1.1)
Co-amoxiclav + Azithromycin + Ceftriaxone + Meropenem	3 (2.1)

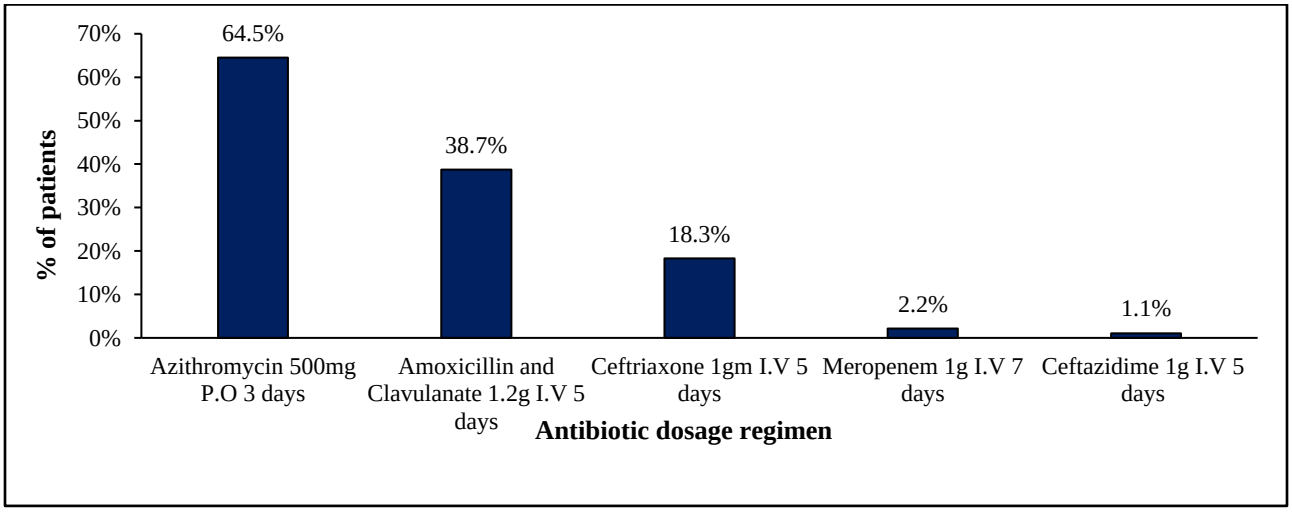

Figure 1: Most prescribed antibiotic dosage regimens.

Association between comorbidities and antibiotic use

Table 4 shows that majority of patients with comorbidities were on antibiotics. There was a statistically significant association between patients who had diabetes (30, 83.3%) and the use of antibiotics. All the patients presenting with renal failure and cancer were put on antibiotics.

Table 4: Association between comorbidities and antibiotic use

Comorbidity	Antibiotic prescribed	Frequency, n (%)	p-value
Diabetes	Yes	30 (83.3)	**0.018**
	No	6 (16.7)	
Hypertension	Yes	27 (77.1)	0.154
	No	8 (22.9)	
Human immunodeficiency virus	Yes	5 (62.5)	0.761
	No	3 (37.5)	
Asthma	Yes	3 (75)	0.742
	No	1 (25)	
Obesity	Yes	3 (75)	0.742
	No	1 (25)	
Renal failure	Yes	3 (100)	0.223
	No	0 (0)	
Cancer	Yes	2 (100)	0.322
	No	0 (0)	
Congestive heart failure	Yes	1 (100)	0.494
	No	0 (0)	

Biomarkers, severity of disease and antibiotic prescribed

As shown in Table 5, all patients admitted to critical care units received an antibiotic during their course of treatment (p= 0.043). In addition, all patients on mechanical ventilation were prescribed an antibiotic (p<0.05). There was a statistically significant association between the severity of COVID-19 disease and antibiotic prescribing. Almost all patients (28, 93.5%) with severe COVID-19 had a high likelihood of antibiotic treatment (p<0.0001) but slightly less than a third (11, 28.2%) of the patients with mild COVID-19 were treated using an antibiotic (p< 0.0001). Patients who had elevated procalcitonin levels were more likely to receive an antibiotic (p=0.008). However, there was no statistically significant association between elevated levels of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) with antibiotic prescribing.

DISCUSSION

The study showed that 67.4% of the COVID-19 patients received an antibiotic during their therapy. This is consistent with a meta-analysis carried out to determine the rate of antibiotic use, where the extent of empiric antibiotic use was determined as 60-100%.[18] Antibiotic prescribing was highest in the age group 60-69 years, with 20(87%) patients in that category receiving an antibiotic, followed by the age group ≥70 years where 77.8% of the patients received an antibiotic. This is similar to a meta-analysis that reported that the prevalence of antibiotic prescribing increased with age.[19]

Among the COVID-19 patients on antibiotics, the most frequently prescribed was azithromycin (78.5%), followed by amoxiclav (69.9%). This finding corroborates a systematic review involving 28,093 COVID-19 patients, where azithromycin was the most prescribed

antibiotic.[20] According to an article on the pharmacology, pharmacokinetics and clinical efficacy of azithromycin with emphasis on COVID-19, azithromycin exhibits in vitro efficacy against the causative agent for COVID-19, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), potentially impacting various stages of its life cycle. Its immunomodulatory characteristics comprise the capacity to decrease cytokine production, preserve the integrity of epithelial cells and prevent lung fibrosis.[21] This might have played a role in the use of azithromycin. In addition, based on its efficacy in simulated controlled tests on other viral illnesses such as Ebola, azithromycin was also used in mitigating SARS-COV-2 effects.[22] Oral azithromycin 500 mg for 3 days was the most prescribed dosage with 64.5% of the patients receiving the drug. It was observed that the duration of therapy for majority of patients was 3 to 5 days. These findings corroborate a retrospective study carried out in a tertiary center in Minnesota where the duration of treatment for patients on antibiotics was 3-5 days.[22]

Table 5: Association between biomarkers, severity of disease and antibiotic prescribing

Variable	Category	Antibiotic prescribed	Antibiotics not prescribed	*p*-value
Severity of COVID-19	Mild	11(28.2%)	28(71.8%)	<0.0001
	Moderate	53(77.9%)	15(22.1%)	
	Severe	29(93.5%)	2(6.5%)	<0.0001
Type of ventilation	High flow nasal cannula	31(83.8%)	6(16.2%)	0.030
	Noninvasive ventilation	27(84.4%)	5(15.6%)	0.019
	Mechanical ventilation	3(100%)	0(0%)	<0.0001
Patient admitted to ICU	Yes	8(100%)	0(0%)	0.043
	No	85(65.4%)	45(34.6%)	
C-reactive protein range	High	31(86.1%)	5(13.9%)	0.336
	Normal	5(71.4%)	2(28.6%)	
Procalcitonin range	Normal	13(92.9%)	1(7.1%)	0.008
	High	0(0%)	1(100%)	
Erythrocyte sedimentation rate range	Normal	3(37.5%)	5(67.5%)	0.640
	High	3(50%)	3(50%)	

COVID-19= Coronavirus disease 2019; ICU= Intensive care unit.

The most prescribed antibiotic combination was amoxiclav-azithromycin in 43(46.2%) patients, followed by azithromycin-ceftriaxone combination (17.2%). A previous study revealed combinations of beta-lactams and macrolides or fluoroquinolones were common in more than half of the COVID-19 patients.[20] One potential rationale for these combinations is their comprehensive coverage of lung infections by pneumococcal, gram negative and atypical bacteria.[24] The increased use of macrolides in these combinations, specifically azithromycin, correlates with antibiotic prescribing patterns in numerous COVID-19 centers in Africa[2]. This may be related to the fact that at the onset of the pandemic, a number of scientific documents described azithromycin as having significant antiviral properties.[21] Despite scientific papers calling for more research concerning the use of this combination, azithromycin was embraced and used widely in COVID-19 patients.[25]

This study established that a majority of the patients (48.6%, n=67) received two antibiotics during their course of treatment, which correlates with a study carried out in Wuhan, China where a majority of the patients, (45%, n=45) were treated with combination therapy.[9] Majority of the patients who received four different antibiotics were being managed in the ICU. One of the probable reasons for this may be that patients in the critical care units accounted for majority of the patients with secondary bacterial infections thus extended coverage was required. This is consistent with a meta-analysis which reported that bacterial coinfection was highest in critically

ill patients with severe COVID-19 and thus require combination antibiotics.[26]

Severity of disease was a key determinant of antibiotic prescribing. Majority of patients with severe COVID-19 (29, 93.5%) received an antibiotic. This is consistent to a study carried out in China which reported that a high antibiotic prescribing rate was common among patients suffering from severe COVID-19. A number of patients with mild to moderate COVID-19 received antibiotics, deviating from the WHO guidelines which stated that for mild or moderate COVID-19, no antibiotic use for therapy or prophylaxis should be initiated in the absence of clinical features associated with a bacterial infection.[19] Therefore, it is possible that majority of the antibiotic prescribing was unwarranted. Such indiscriminate antibiotic prescribing not only poses risks of antibiotic resistance but may also contribute to unnecessary healthcare costs and adverse effects on patients.[27]

It was evident that diabetes and hypertension were the most prevalent comorbidities among the patients at 36 (59.0%) and 35 (57.0%), respectively. A similar study conducted at Wuhan, China revealed that majority of the COVID-19 patients also presented with hypertension and diabetes.[27] Diabetes was mainly linked with antibiotic prescribing, with 30 (83.3%) of diabetic patients receiving an antibiotic, followed by hypertension (27, 77.1%). Blood glucose levels are thought to have a critical role in the emergence of infectious illness. Anomalies in blood glucose levels may lead to alterations in the immune system of individuals with diabetes, causing dysregulation and diminished immune responses. As a result, the diabetic patients may become vulnerable to SARS-COV-2 and various bacterial infections.[29]

COVID-19 has been associated with conditions involving both immunodeficiency and hyperinflammation. In COVID-19, there is typically a rapid and substantial elevation in serum C-reactive protein (CRP) levels during the acute inflammatory responses.[30] Initially CRP was recommended as a biomarker for excluding bacterial complications or co-infections in COVID-19 patients during the early stages of the pandemic but later demonstrated limited diagnostic efficacy as it lacked specificity for bacterial infections.[31] Suffice to note, 86.1% of the patients that had their CRP determined received an antibiotic. This is consistent with a study that reported that the most common biomarker used to support antibiotic use in COVID-19 patients was CRP.[32] Procalcitonin test, deemed more prognostically valuable, was not routinely conducted with only 15 (10.9%) of the patients subjected to the test.

Although this study shows interesting findings in the use of antibiotics among the COVID-19 patients, we appreciate a few limitations. The KNH, being a referral facility, received several patients referred to the hospital after management in other facilities where antibiotics had already been administered. This might have reduced the prevalence of antibiotic prescribing found in the present study as only patients for whom antibiotic was prescribed in KNH were included. During data collection, some of the files were missing data. However, this was minimized by ensuring that majority of the files picked were legible and had most of the information required.

CONCLUSION

There was a high prevalence of antibiotic prescribing in the management of COVID-19 patients, principally with azithromycin and co-amoxiclav. Severity of disease, admission type, age of the patients and elevated C-reactive protein were significantly associated with antibiotic prescribing among patients. Clinicians mostly used antibiotics based on the severity of COVID-19 disease and presence of comorbidity. Further research is needed to ascertain the long-term effects of antibiotic use in COVID-19 patients. Additional investigations are necessary to establish the survival rates based on the absence or presence of empirical antibiotics in managing COVID-19.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the staff at KNH's Infectious Disease Unit for logistical support during data collection.

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