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The Effect of Antibiotics and Drugs on the Duration of COVID-19 in Hospitalized Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

This is a single center, retrospective, observational study carried out in Ohud hospital, the main referral hospital for SARS-CoV-2 infections in the region of Madinah, Kingdom of Saudi Arabia. The study was carried on hospitalized patients with moderate to severe symptoms, including critically ill patients in the intensive care unit mostly of them requiring oxygen or mechanical ventilator support. Medical records from 432 cases were investigated showing that the majority of infected population were adults with an average age of 48 years, where 68.3% were males and the mortality rate was 5.6%. Duration of the disease was determined as the period between the first positive and the first negative PCR results. Patients who received antibiotics or Metoclopramide showed shorter duration of the disease time course while those who received Hydroxychloroquine, Omeprazole or Calcium exhibited longer durations before obtaining a negative PCR result. Regression analysis furtherly confirmed that antibiotics administration was associated with shorter course of disease while hydroxychloroquine or omeprazole were correlated with longer duration of the disease. Antiviral drugs, however, showed no correlations to the COVID-19 duration of stay in hospital. Finally, combining antibiotics and antiviral agents did not result in a better outcome, suggesting that the use of antibacterial agents helps in the recovery of SARS-CoV-2 patients.

Keywords: COVID19; SARS-CoV-2; antibiotics; antibiotics; Saudi Arabia.

1. INTRODUCTION

Coronaviruses are a groups of RNA viruses belonging to the family *Coronaviridae* capable of infecting humans and animals [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an infection which started in the province of Wuhan in China towards the end of 2019 [2] and caused a worldwide pandemic which continues to infect millions around the world. As per today, more than 219 million cases have been reported with a mortality rate of around 4%. While the virus continues to claim the lives of more than a million, no treatment was yet shown to eradicate the virus effectively. The clinical features of the SARS-CoV-2 illness ranges from mild to critically ill. The mean incubation period is around 5 days [3], while the main symptoms were fever, cough, shortness of breath, and myalgia or fatigue and diarrhea. Currently, most the medication given to hospitalized patients are to manage the symptoms and to decrease the severity of the disease. However, a number of patients require respiratory assistance therapy to help them pass the acute phase of the disease. Respiratory infection is commonly associated with co-infections [4, 5]. Generally, secondary bacterial co-infections with viral infections contributes to the reported increase in mortality of affected patients [6, 7]. We therefore investigated the effect of adding antibiotics to the treatment regimen of COVID19 patients and compared the outcome to patients who did not take any antibiotics. Secondary bacterial infections during pandemics are known to contribute significantly to morbidity specially in individuals with high risk, such as those with chronic disease and immunocompromised patients [8]. Recent studies suggest that COVID-19 infections are commonly accompanied with bacterial co-infections [9, 10]. The combination of hydroxychloroquine and azithromycin has been extensively used in many countries, after an early report from France in March 2020 showed that the combination can be beneficial for patients with SARS-CoV-2 infections [11], however, the effect of azithromycin alone was not evaluated. Other reports from China also confirmed the usefulness of hydroxychloroquine [12]. However, this was overturned by many other reports [13-15], and the current mainstream is not to use hydroxychloroquine for COVID19. Azithromycin has been at the forefront of the antimicrobial agents used in COVID19. Several mechanisms have been suggested, beside its well documented action as a macrolide antibiotic acting as a protein synthesis inhibitor, azithromycin was also suggested to have beneficial anti-inflammatory effect against the inflammatory mediators most reportedly to be involved in SARS-CoV-2 pathology, the interleukin 6 (IL-6) as previously reported, and other inflammation mediators [16-20]. As a global public health emergency, it is important to recognize the possible role of medications on the outcome of the disease. The aim of the study was to analyze the data obtained from hospitalized patients retrospectively to explore the possible contribution of certain drug or class of drugs on the duration of the disease, and this was the main focus of this study.

2. MATERIALS AND METHODS

2.1 Data Collection

This was a single center retrospective observational study conducted in the referral hospital for COVID19 (Ohud hospital) in the region of Madinah, in the west of Saudi Arabia. Ohud hospital is the COVID19 reference center in the region serving a number of cities and villages within the region. The hospital was receiving patients suspected to have SARS-CoV-2 infection exclusively. Cases were triaged in the emergency department; mild cases were sent to isolation accommodations prepared specially for the pandemic, and patients with moderate to severe symptoms requiring hospitalization were admitted. According to initial visual triage score, mild infections including fever and common cold-like symptoms were sent home for self-isolation, only patients with respiratory symptoms were admitted to hospital (moderate) and those who required mechanical ventilation were classified as severe. Sample size was calculated (confidence level 95%) according to the population of the area of Madinah area (2 million) to be 385. Data were collected for 432 patients admitted to the hospital in June-August 2020. The study was retrospective and carried out on hospitalized patients' records. Patients included in this study were all having moderate to severe or severe SARS-CoV-2 infection. Duration of the disease was calculated from the first polymerase chain reaction (PCR) positive result until the first negative PCR result. The hospital PCR screening was carried every 3 days or upon relief of symptoms. Most of patients were on either high flow oxygen support or on a mechanical ventilator. Only adults were included.

2.2 Drugs and Medication

All used drugs were recorded and classified according to pharmacological use. Antibiotics administrated to the patients in this study were mainly Azithromycin, Linezolid for gram positive resistant bacteria, third generation cephalosporins (Ceftriaxone), Imipenem/Cilastatin, broad spectrum antibiotics such as Meropenem and fluoroquinolones including ciprofloxacin and Moxifloxacin or any combination of those antibiotics. Additionally, antiviral drugs, non specific to SARS-CoV-2 infections were studied. Antiviral drugs used were mainly Oseltamivir, Ritonavir and Acyclovir in few cases. Medications given to chronic diseases were also included such as beta blockers (BB), angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEi), statins (Atorvastatin and Rosuvastatin) and oral hypoglycemic drugs (metformin). A range of drugs was used which varied according to the need of each patient. Those included antifungal drug (caspofungin), dexamethasone and hydroxycortisone which was used for late stages of severe pneumonia, enoxaparin was given to protect from blood clotting events and lastly paracetamol for fever among others.

2.3 Statistical Analysis

Descriptive statistics are presented in the form of minimum, maximum, median, mean and standard deviation, while categorical variables are presented in the form of frequencies and relative frequencies. Comparison of the duration of stay across groups of patients who received the medications and those who did not was done using independent t-test. Multiple linear regression was used to control for different variables when studying the association between given medications and the duration of stay. IBM SPSS 26 for windows was used for the statistical analysis and p-value <0.05 is considered significant.

3. RESULTS

3.1 Descriptive Data of the Patients

The data from the records of 432 patients were studied. All patients were having mild to severe infection, requiring hospitalization according to the COVID19 management protocols of the Ministry of Health in Saudi Arabia. The youngest patient was 10-month-old infant, and the oldest was a 101 years old woman, however, only adults were included in the analysis. The mean age was 48.5 years showing that moderate to severe infection requiring hospitalization affected mostly population in their late 40s, and with a standard deviation of 17.4 years, the numbers showed that patients younger than 31 years old commonly had mild symptoms and did not require admission to hospital (Table 1). The virus seemed to infect males more than females, at least in the Madinah area where the study was carried out. The data shows that the majority of cases (68%.3) were males with an overall mortality rate of 5.6% (Table 2).

Table 1. Age of COVID19 patients and duration of disease

	N	Median	Minimum	Maximum	Mean	SD
AGE (Years)	432	48	20	101	48.5	17.4
DURATION (DAYS)		9	1	65	11.8	9.7

Table 2. Sex and final outcome in COVID19 patients

Sex	N	%
Females	137	31.7
Males	295	68.3
Outcome		
Expired	24	5.6
Recovered	408	94.4

3.2 Medications Given to Patients

Most patients received the main medications recommended by the Ministry of Health in Saudi Arabia. The main drugs used were paracetamol, antibiotics, antiviral drugs and anticoagulants. However, other drugs have been used to manage individual requirements and varied according to each case, for example, antifungal drugs were used in case of secondary fungal infections, omeprazole to minimize the side effects of other drugs on the gastrointestinal tract (GIT), angiotensin receptor blockers (ARBs) and beta blockers (BB) and Angiotensin converting enzyme inhibitors (ACEi) for patients with cardiovascular diseases, statins for hyperlipidemic patients, bronchodilators and corticosteroids for patients with severe pneumonia and other vitamins and supplements for those in need. Medications were classified into classes as specified in Table 3. Antibiotics were the most used drugs, with Azithromycin as the first choice. Amoxicillin was also used in many cases, along with other antibiotics which varied from case to another, including Cephalosporins and protein synthesis inhibitors such as Linezolid depending on the lab results. More than 90% of the patients required the use of an antibiotic, while antiviral drugs were used in 29.9% of patients. Anticoagulants were used in 88% of the patients as a thromboembolic prophylactic, mainly, enoxaparin I.V. injections were used. Omeprazole was also used in a 67.4% of patients (291 out of 432) and for patients with fever, paracetamol was given to 45.4% of patients and Aspirin to 10.6%. The details of all given medications are shown in Table 3.

3.3 Correlation between Given Medications and the Duration Course of the Illness

The duration of the disease was calculated from the first day on which a positive PCR was confirmed until the first negative PCR result. PCR was carried out every 3 days for all hospitalized patients included in this study. To study the effect of a drug on the time course of the disease, data were categorized into two groups; patients who have taken a drug (medication given) versus patients who did not take this particular drug, or class of drugs (medication not given). The mean time was around 11 days for moderate to severe SARS-CoV-2 patients requiring hospitalization. P-value is significant for the medications: antibiotics, Hydroxychloroquine, Omeprazole, Calcium, and Metoclopramide. It was evident that patients taking antibiotics exhibited shorter course of SARS-CoV-2 infection. Those patients required 3.4 days less to obtain a negative PCR result, and hence, to be released from hospital. Hydroxychloroquine use, however, showed a correlated 5 days longer stay at hospital. The use of omeprazole was associated with 3.8 days increase in the duration course of the disease. The administration of calcium supplements was associated with patients who stayed more time in hospital, however, only 9.6% of patients were on calcium while metoclopramide showed shorter duration of illness. All other taken medication showed no effect on the duration course of the disease as detailed in Table 4.

3.4 Linear Regression Analysis

Multiple linear regression analysis for the duration of stay controlling for age, sex, outcome and other medications. After controlling for other variables, the only medications associated with the duration of stay were antibiotics, hydroxychloroquine and omeprazole. Receiving antibiotics was associated with shorter duration while receiving hydroxychloroquine or omeprazole was associated with longer duration (Table 5).

Table 3. Medication given to patients

Given Medications	N	%
Antibiotics	392	90.7
Metronidazole	31	7.2
Antifungal	21	4.9
Antiviral	129	29.9
Paracetamol	196	45.4
Corticosteroids	116	26.9
Hydroxychloroquine	25	5.8
Insulin	46	10.6
Omeprazole	291	67.4
Anticoagulant	380	88.0
Antiplatelets	20	4.6
Aspirin	46	10.6
H2 blockers	13	3.0
ACEi	21	4.9
ARB	6	1.4
BB	45	10.4
Diuretics	36	8.3
Statins	58	13.4
Antihistamine	13	3.0
Kcl	27	6.3
CCB	79	18.3
Clacium	46	10.6
CVS	4	0.9
Vit D	25	5.8
Vit B	23	5.3
Multivitamins	11	2.5
Iron	25	5.8
Folic acid	9	2.1
Inhaled corticosteroid	41	9.5
Bronchodialtor	65	15.0
Norepinephrine	33	7.6
SMR	13	3.0
Metoclopramide	10	2.3
Mucolytic	9	2.1
Antidiabetic	4	0.9
Antitussive	4	0.9

Multiple linear regression was used to control for the age, gender, outcome and other given medications. After controlling for other variables, the only medications associated with the duration of stay were antibiotics, hydroxychloroquine and omeprazole. Receiving antibiotics was associated with shorter duration (an average of 3.5 days shorter, 95% CI is -6.7, -0.3) while receiving hydroxychloroquine or omeprazole was associated with longer duration, an average of 4.9 (95% CI: 1.05, 8.82) and 3.8 (95%CI: 1.79, 5.84) days longer, respectively.

3.5 Combination of Antibiotics and Antiviral or Anticoagulant Drugs

Comparison of patients who received antibiotics alone to those who received antibiotics with antivirals was carried out (Table 6). Comparison of the length of stay in days between the two groups showed no significant difference; the length of stay at hospital for patients administrating antibiotics was 12.2 while those on antibiotics combined with antiviral drugs stayed for 10.74 days (P=0.187). Comparison of patients who received antibiotics alone to those who received antibiotics with Anticoagulants was also carried out to find any correlations between the two mostly used drugs (Table 7). Comparison of the length of stay in days between the two groups showed no significant differences (P=0.087).

Table 4. Relationship between the duration of the disease and the given medications

Drug	Medication not given			Medication given			P-value
	N	Mean	SD	N	Mean	SD	
Antibiotics	40	14.8	10.2	392	11.5	9.6	**0.041**
Metronidazole	401	11.9	9.9	31	10.7	7.2	0.529
Antifungal	411	11.7	9.9	21	12.7	5.4	0.664
Antiviral	303	12.1	10.0	129	10.9	8.9	0.229
Paracetamol	236	11.7	10.0	196	11.8	9.4	0.949
Corticosteroids	316	11.3	9.4	116	13.0	10.3	0.739
Hydroxychloroquine	407	11.5	9.7	25	16.5	9.0	**0.011**
Insulin	386	11.8	9.5	46	11.8	11.0	0.966
Omeprazole	141	9.2	7.1	291	13.0	10.5	**<0.001**
Anticoagulant	52	10.4	8.4	380	12.0	9.9	0.273
Antiplatelets	412	11.6	9.6	20	14.3	11.1	0.233
Aspirin	386	11.6	9.4	46	13.4	12.2	0.335
H2 blockers	419	11.8	9.8	13	11.0	8.2	0.772
ACEi	411	11.5	9.6	21	16.4	11.6	0.073
ARB	426	11.8	9.7	6	12.7	7.3	0.820
BB	387	11.5	9.7	45	13.7	9.7	0.156
Diuretics	396	11.7	9.7	36	12.3	9.3	0.743
Statins	374	11.4	9.1	58	14.4	12.9	0.087
Antihistamine	419	11.7	9.6	13	14.6	12.5	0.283
Kcl	405	11.7	9.7	27	13.1	10.2	0.471
CCB	353	11.4	9.4	79	13.6	10.8	0.064
Calcium	386	11.4	9.7	46	14.5	9.6	**0.043**
CVS	428	11.7	9.7	4	19.0	12.5	0.134
Vit D	407	11.6	9.3	25	15.2	14.3	0.221
Vit B	409	11.8	9.8	23	10.3	6.9	0.471
Multivitamins	421	11.7	9.7	11	15.2	10.6	0.238
Iron	407	11.8	9.8	25	11.6	8.1	0.946
Folic acid	423	11.8	9.7	9	11.6	8.7	0.947
Inhaled corticosteroid	391	11.8	9.9	41	11.2	7.0	0.679
Bronchodilator	367	11.9	10.0	65	11.1	7.6	0.524
Norepinephrine	399	11.7	9.5	33	12.2	12.0	0.799
SMR	419	11.8	9.8	13	10.0	5.6	0.505
Metoclopramide	422	11.8	9.8	10	9.2	2.1	**0.004**
Mucolytic	423	11.8	9.8	9	11.3	5.2	0.892
Antidiabetic	428	11.8	9.7	4	13.8	2.9	0.682
Antitussive	428	11.8	9.7	4	12.8	8.5	0.839

Table 5. Linear regression analysis of variables

	Coefficients	P-value	95.0% Confidence Interval for the coefficient	
AGE	0.0	0.752	-0.1	0.0
Gender	1.0	0.306	-0.9	3.0
Outcome	-3.7	0.072	-7.7	0.3
Antibiotics	-3.3	**0.041**	-6.4	-0.1
Hydroxychloroquine	4.9	**0.013**	1.1	8.8
Omeprazole	3.8	**<0.001**	1.8	5.7
ACEi	2.3	0.308	-2.2	6.8
BB	0.3	0.883	-3.1	3.6
Statins	1.6	0.289	-1.3	4.5
CCB	1.0	0.426	-1.5	3.5
Calcium	2.1	0.189	-1.0	5.1
CVS	3.6	0.469	-6.2	13.4
Metoclopramide	-2.9	0.338	-9.0	3.1

Table 6. The relation between antibiotics alone and the effect of antibiotics and antiviral drugs together

Antibiotic alone			Antibiotic with antiviral			P-value
N	Mean	SD	N	Mean	SD	
243	12.20	10.335	118	10.74	8.726	0.187

Table 7. The relation between antibiotics alone and the effect of antibiotics and anticoagulant drugs together

Antibiotic alone			Antibiotic with anticoagulant			P-value
N	Mean	SD	N	Mean	SD	
34	8.9	7.7	327	12.0	10.0	0.078

4. DISCUSSION

To the best of our knowledge, this is the first retrospective study to describe the importance of administrating antibiotic medications in reducing the staying time of hospitalized COVID-19 patients in Saudi Arabia. All PCR confirmed COVID-19 cases from Ohud Hospital, Madinah, Kingdom of Saudi Arabia, were included in this study, ranging from moderate to severe symptoms and requiring hospitalization. Evidence for an association of viral infection and co-infection with bacteria was evident from previous studies [4]. Secondary bacterial co-infections contribute to increasing the mortality rate among infected patients due to immune system dysfunction (Jia L. et al, 2020). For example, a secondary bacterial infection following influenza was found to increase the severity of the illness and death rate [21]. In addition, it was recently reported that a large number of patients with COVID-19 were co-infected with bacteria [10]. Examples of those bacteria pathogens isolated from COVID-19 patients include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* [22]. Therefore, considering antibiotic medications in the treatment plan for those patients is critical to reduce the severity of complications. The Ohud hospital team followed the Saudi Ministry of Health protocols that included antibiotics such as azithromycin, fluoroquinolones and Linezolid. Our data showed that the average staying time for COVID-19 patients who received antibiotic medications was shorter than those patients who did not take any antibiotics. This may indicate the role of antibiotic in treatment of COVID-19 patients with respiratory difficulties. Antibiotic medications can help eradicate the pathogens responsible for bacterial secondary infections, in addition, antimicrobial agents are shown to have anti-inflammatory effects against some cytokines and other mediators that cause respiratory complications [23, 24]. Our data was consistent with what Gautret and his colleagues found, that adding azithromycin to the management plan for COVID-19 patients helped with in the resolution of the symptoms [11]. However, overuse of antibiotics may feed the bacterial resistance mechanisms. Therefore, proper selection of antibiotics with narrow spectrum might reduce this problem. In addition, antibiotics are given empirically to COVID-19 patients, thus antibiotics should be stopped for those who tested negative for bacterial infection. Another important finding in this study is that COVID-19 patients who received Hydroxychloroquine (An anti-malaria drug) or Omeprazole (A proton pump inhibitor drug) stayed in the hospital for longer duration. A recent evidence from clinical trials suggested that hydroxychloroquine is ineffective in COVID-19 treatment [25]. Moreover, FDA had ended the emergency use of hydroxychloroquine as it is ineffective and may cause serious cardiac side effects [26]. Further tests for hospitalized COVID-19 patients are needed to understand the reasons for staying longer for those who were receiving hydroxychloroquine. In one study, it was shown that administration of hydroxychloroquine as postexposure prophylaxis will not prevent the COVID-19 infection when it was compared to a placebo group [27].

Omeprazole is a member of the proton pump inhibitors (PPIs) group mainly used for gastrointestinal conditions associated with increasing gastric acid secretion [28]. The side effects of PPIs are generally tolerable, however, if it was used for long term, which may lead to complications such as hypochlorhydria [28]. Patients with COVID-19 are prescribed PPIs in order to reduce the effects of the several administrated drugs on the stomach. It has been found that using PPIs are associated with the increase of the risk of pneumonia [29]. This may

explain why our COVID-19 patients who were given omeprazole endured a longer duration of the disease. Moreover, omeprazole may contribute to increase the alkalinity of the stomach which may affect their ability to eradicate pathogens and ultimately lead to a secondary infections [30]. Collectively, because SARS-CoV-2 infection can result in decreased immunity, it is probable that bacterial superinfection can further complicate the morbidity of the disease and result in longer stay in hospital and persistence of symptoms. It is, therefore, recommended to use antimicrobial agents for moderate to severe infections of SARS-CoV-2 to protect from co-infections [31].

5. CONCLUSION

This retrospective analysis showed that drugs used for hospitalization of COVID-19 patients correlates to the duration of the disease time course, providing useful information for updating the treatment protocols. Further research on a larger number of patients and clinical research are required to confirm these results. The results are expected to support the use of specific drugs for COVID19 patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study protocol for research involving humans was in accordance to guidelines of national research ethics regulations and according to the Declaration of Helsinki. Ethical approval was obtained from the institutional review board (IRB 553), General Directorate of health affairs in Madinah, under the number: H-03-M084, and the study was granted ethical clearance by the hospital.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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