A Retrospective Study on the Pattern of Antibiotic Use Among Hospitalized Patients with COVID-19 Infection (SARS-Cov-2 Omicron Variant) in a Referral Hospital in the Sultanate of Oman

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Received: 23 January 2024

Accepted: 28 December 2024

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DOI 10.5001/omj.2025.53

Abstract

Objectives: Overuse of antibiotics was widely reported during COVID-19 pandemic and there was an accelerated threat of antimicrobial resistance. There are only limited studies which evaluated the prevalence and pattern of antibiotic use during the Omicron phase of the pandemic The present study aimed to identify and evaluate the prescribing pattern of antibiotics among hospitalized patients with SARS-CoV-2, Omicron variant in Royal Hospital, Sultanate of Oman.

Methods: This was a retrospective study based on data obtained from hospitalized patients with COVID-19 caused by SARS-CoV-2 Omicron variant from December 2021 till February 2022. The data was collected from the Royal Hospital electronic record system and evaluated for prevalence and pattern of antibiotic use. Patients' demographic and clinical details (COVID-19, co-morbidities and simultaneous infections), details on patients' hospital stay and outcome were collected and evaluated. Association between simultaneous infection, antibiotic use and patient, and disease characteristics were done. Statistical analysis was done using R software and association between categorical variables were tested using Chi-square test.

Results: A total of 176 hospitalized patients were included. The mean age was 59.3±18.6 and majority (123, 69.9%) of the patients had mild disease followed by those with severe disease (40, 22.7%). Among the included patients, simultaneous infection (coinfection or superinfection) was present in only 11 (6.3%) and was caused by bacteria in 7 patients. Fifty-nine percent (n=104) of total patients received antibiotics during their stay in the hospital, though, a confirmed bacterial simultaneous infection (based on culture results) was found only in 7 (6.7%) of the patients. Most patient received ceftriaxone (45.2%) and piperacillin and tazobactam (45.2%) followed by vancomycin (21.2%). Antibiotics were used for only one day to three days in half of the patients. Median duration of antibiotic use in an individual patient was 4 days (1- 16). Statistically significant difference was observed between the status of antibiotic use and gender (p=0.03), and presence of simultaneous infection (p=0.029). A significant association was noted between number of antibiotics used and duration of antibiotic treatment with various patient and disease characteristics.

Conclusion: Among the COVID-19 patients caused by SARS-CoV-2 Omicron variant, confirmed simultaneous infection was observed only in few patients though antibiotics were used widely in more than half of the patients. There is a definite need to implement effective antimicrobial stewardship program during such unprecedented times to avoid consequences of antibiotics overuse including antibiotic resistance.

Keywords: Antibiotics, COVID-19, SARS- CoV-2 Omicron variant, Sultanate of Oman.

Introduction

Corona virus infectious disease 2019 (COVID-19) was first recognized in China, then gradually spread globally. In Oman starting from 3rd of February 2020 until 16th of September 2022, according to World Health Organization (WHO) 397,993 cases of COVID-19 have been reported with 4,628 deaths. [1] During the initial phase of the COVID-19 pandemic, antibiotics were commonly used for the disease treatment, most often empirically.[2] This was influenced by the experiences from the H1N1 influenza pandemic in 2009 that indicated the high rate of secondary bacterial infections in patients admitted to the intensive care unit (ICU).[3-5] Later concerns regarding the overuse of antibiotics and concerns of resistance emerged. It was hypothesised that the COVID-19 pandemic may be accelerating the threat of antimicrobial resistance (AMR) due to the increased use of antibiotics, increased exposure to hospital environments and invasive procedures used in COVID-19 treatment. At the same time the evidence for the benefits of antimicrobial use in such patients was limited.[6]

A scoping review conducted based on 118 studies reported that a large proportion (40–50%) of antibiotic prescribing for COVID-19 patients did not have clinical indications. [6] In a systematic review and meta-analysis conducted by Al Shaik based on studies from January 2020 and June 2021 pooled estimates for the prevalence of bacterial co-infection and antibiotic use were 5.62 and 61.77%, respectively.[7] Patients without clinical evidence of bacterial co-infection should not receive antibiotics treatment according to international guidelines. The evidence suggest that if secondary bacterial infection is absent, antibiotic prescribing may not be beneficial for treatment outcomes in COVID-19 patients.[6]

Recommendation on the use of antibiotics among COVID-19 patients were frequently updated by the National Institutes of Health [8] Unites States of America and the same were followed as National recommendations in Oman. Among patients with moderate or severe illness, if bacterial pneumonia is suspected, administering empiric antibiotic treatment is recommended, with re-evaluation of the patient daily. In critically ill adult patients with severe or critical COVID-19 and in the absence of suspected or proven bacterial infection, avoiding the use of empiric broad-spectrum antibiotics is highly recommended. Antibiotic use may be considered in conditions suggestive of sepsis, septic shock, or bacterial pneumonia. Antibiotics used for treatment of patients with critical or severe COVID-19 should follow the guidelines for other hospitalized patients with ventilator-associated pneumonia, hospital acquired pneumonia, or any other type of hospital acquired infection. [8]

Various antibiotics were used during the pandemic in different groups of COVID-19 patients. It is important to understand the prevalence, pattern as well as the appropriateness of the use of antibiotics in patients with COVID-19 in any health care setting. Furthermore, it is interesting to understand the pattern of use of these antibiotics at various waves of the pandemic and the factors which influenced their prescribing. Evaluating the specific details of this sort will be helpful to understand the rationality of use of the antibiotics at various waves and will help to understand areas for the improvement of antibiotic prescribing in similar situations.

A single center study conducted by Pandak et al. retrospectively analyzed the four years data (2018–2021)) to assess antibiotics use before and during the COVID-19 pandemic and correlate the results with the rate of resistant microorganisms detected in hospitalized patients during the study period. [9] Within the limitations of the above study, correlation analysis suggests that the overuse of broad-spectrum antibiotics resulted in a significant increase of AMR, and this effect was seen over a rather short time. The number of studies which specifically evaluated the pattern of antibiotic use among COVID-19 patients in Oman is limited. [11, 12] There are only limited studies which evaluated the prevalence and pattern of antibiotic use during the Omicron phase of the pandemic. [10] The present study aims to identify and evaluate the prescribing pattern of antibiotics among hospitalized patients with COVID-19 caused by SARS-CoV-2, Omicron variant.

Methods

This was a retrospective study based on data from hospitalized patients with COVID-19 caused by SARS-CoV-2 Omicron variant in the Royal Hospital, Sultanate of Oman. Approval for the study was obtained from the Scientific Research Committee of Royal Hospital (SRC #26/2020). Royal Hospital is a 1200 bed tertiary-level, acute-care hospital in Muscat. During COVID-19 pandemic, Royal Hospital was a major health care setting which was involved in treating COVID-19 patients with disease severity of mild,moderate, severe and critical. Study population included hospitalized patients in Royal Hospital with a diagnosis of COVID-19 infection (Omicron variant) from December 2021 till February 2022 according to the COVID-19 registry maintained by the Infectious disease department of the hospital.

The data was collected from the electronic hospital record system of the hospital. The inclusion criteria for the study were all COVID-19 hospitalized patients whose diagnosis was confirmed on either a positive SARS-COV2 PCR or rapid antigen test of the nasopharyngeal swab,those patients whose age is over than 18 years old,has been hospitalized for more than 24 hours, and the variant of the SARS-CoV-2 was reported as Omicron variant in the registry maintained by the infectious disease department of the hospital. Patients of all nationality were included in the study.

Exclusion criteria included cases under 18 years of age, discharged from the emergency room, or discharged or died within 24 hours of hospitalization and cases reported as variants other than omicron.

The parameters for evaluation

Prevalence and pattern of antibiotic use: type of antibiotics, number of antibiotics used in each patient, duration/dose and route of administration of antibiotics used, reported or assumed indication for use of antibiotics, the pattern of use in ICU and non-ICU cases.

Patient and COVID-19 disease characteristics: Patient characteristics (age, gender, presence of comorbidities like diabetes mellitus, hypertension, asthma or others.) of those who were prescribed with antibiotics vs non users were assessed. Disease details including severity, status of stay in ICU, length of hospital stay, and outcome at 14 days were documented. For severity, the cases were classified as mild, moderate -, and severe based on the classification as per the 'Living guidance for clinical management of COVID-19' published by WHO.[13] Mild disease are reported as symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. Moderate disease as adults with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air. Severe as adults with clinical signs of pneumonia (fever, cough, dyspnea) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air. For the purpose of the study the critical cases as per definition were included in the severe category Outcomes in the patients were classified as mortality, remains hospitalised and recover.

Details of simultaneous infection present: In the present study, positive blood (b/c), urine (u/c), and endotracheal aspirate cultures (ET/c) were considered to be possibly COVID-19 related while other positive cultures were considered unrelated.

Infections which were present along with COVID-19 infection were considered as simultaneous infection and they were categorized as either 'coinfection' or 'hospital acquired infection/superinfection'. Clinically significant positive culture that were sampled within the first 48 hours of the admission were categorized as coinfection while those sampled after the first two days of the hospital stay were labelled as hospital-acquired infection /Superinfection**.**[12] Individual patient cases were assessed for the presence or absence of simultaneous infection (Co-infection and Superinfection/Hospital Acquired infection), nature of simultaneous infection, and type of the organism isolated.

Further, association between antibiotic use and presence of simultaneous infection with patient and disease characteristics were done using suitable statistical analysis. Statistical analysis

The obtained data was evaluated using descriptive analysis and statistical analysis was conducted using R software version 4.2.2, R Core team, Austria. Association between categorical variables were tested using Chi-square test. $p < 0.05$ were considered statistically significant.

Results

A total of 225 patients from the COVID-19 registry, hospitalized in the Royal Hospital were considered for inclusion. Based on the inclusion and exclusion criteria, 176 (78.2%) patients with COVID-19 infection (Omicron variant) were included. Forty-nine patients were excluded due to incomplete and missing data, duplicated patient forms, and discharge before completing 24h in hospital and patients under 18 years old.

Demographic and details of the patients are summarized in Table 1. Maximum number of patients were in the age group 61-75 years (n=54, 30.7%) and 59.7% (n=105) of patients were males. Most of the patients had at least

one co-morbidity (n=139, 79.0%), hypertension (n=58,33.1%) being the most common followed by diabetes mellites (n=43, 24.5%). Majority (n=123, 69.9%) of the patients had mild disease followed by those with severe disease (n=40, 22.72%). Thirty three (18.8%) of patients were admitted in the ICU. Demographics and outcome (at 14 days) of the patients admitted in ICU are represented in Table 2. Among them highest percentage (46%) were in the age group above 60 and in 59% of them death was the final outcome at 14 days. Most of the patients stayed in the hospital either for 1-3 or 4-6 days. When evaluating the 14-day patients' outcome, majority of them recovered (n=122, 69.3%) while 29 (16.5%) died.

Table 1: Patient demographics and clinical characteristics.

Parameters	**No. (%)**
Gender	
Male	105 (59.7)
Female	71 (40.3)
Age group	
18-30	13 (7.4)
31-45	33 (18.8)
46-60	37 (21.0)
61-75	54 (30.7)
> 75	39 (22.2)
Presence of co-morbidities	
Yes	139 (79.0)
No	37 (21.0)
Severity of COVID-19 infection	
Mild	123 (69.9)
Moderate	13 (7.4)
Severe	40 (22.7)
Stayed in ICU	
Yes	33 (18.8)
No	143 (81.3)
Total length of stay in the hospital (in days)	
1-3	61 (34.7)
4-6	60 (34.1)
7-9	15 (8.5)
10-12	13 (7.4)
>12	27 (15.3)
Outcome at 14 days	
Death	29 (16.5)
Recovered	122 (69.3)
Remains hospitalized	25 (14.2)

Table 2: Demographics and clinical outcomes of patients admitted in the ICU.

Parameters	**No. (%)**
Age	
18-30	1 (3%)
31-45	9 (22%)
46-60	12 (29%)
>60	19 (46%)
Gender	
Male	20 (73%)
Female	11(27%)
Outcomes at 14 days	
Recovery	17(41%)
Mortality	24(59%)

Out of the 176 included patients, only 11 (6.3%) had simultaneous infection. Confirmed bacterial infection was present in 7 patients ,while *Candida* spp was detected in in the remaining 4 patients. Table 3.

Table 3: Common organisms isolated from COVID 19 patients with co infections and super infections.

Parameters	**Total No. (11)**
Type of organisms	
Bacterial	7
Fungal	4
Details of organism Bacteria	
E. coli	2
Enterobacteriaceae	2
Pseudomonas aeruginosa	2
Stenotrophomonas maltophilia	1
Staph. aureus	1
Fungus	
Candida spp.	4
Diagnosis of infection	10 (90.9)
Sepsis urinary tract infection	2 (18.2)
Catheter related blood stream infection	1 (9.1)
Pneumonia	1 (9.1)

The most common type of the infection was sepsis among the patients who had confirmed simultaneous infection, 5 were coinfection while the remaining 6 were superinfection or hospital acquired infection.

A total of 104 (59.1%) patients received at least one antibiotic during their stay in the hospital, though a confirmed simultaneous infection (based on culture results) was found only in 11 patients. Among these 104 patients, most commonly used antibiotics were ceftriaxone (45.2%), piperacillin and tazobactam (45.2%) followed by vancomycin (21.2%) as it is presented in Table 4. All antibiotics were administered intravenously (IV) expect 2 were given orally (azithromycin, doxycycline).

Table 4: Common antibiotics used in patients with COVID-19.

Antibiotic	**No. (%)**
Ceftriaxone	47(45.2%)
Piperacillin+Tazobactam	47(45.2%)
Vancomycin	22 (21.2%)
Meropenem	16(15.4%)
Amoxicillin+clavulanic acid	15 (14.4%)
Amikacin	1 (0.96%)
Azithromycin	1 (0.96%)
Clarithromycin	1 (0.96%)
Doxycycline	1(0.96%)
Gentamicin	1(0.96%)

Considering the duration of antibiotic use among the 104 patients who received antibiotics, 49%, (n=51) of patients received antibiotics for 1-3 days and 33.7%(n=35) were treated for 4-6 days [Figure 1].

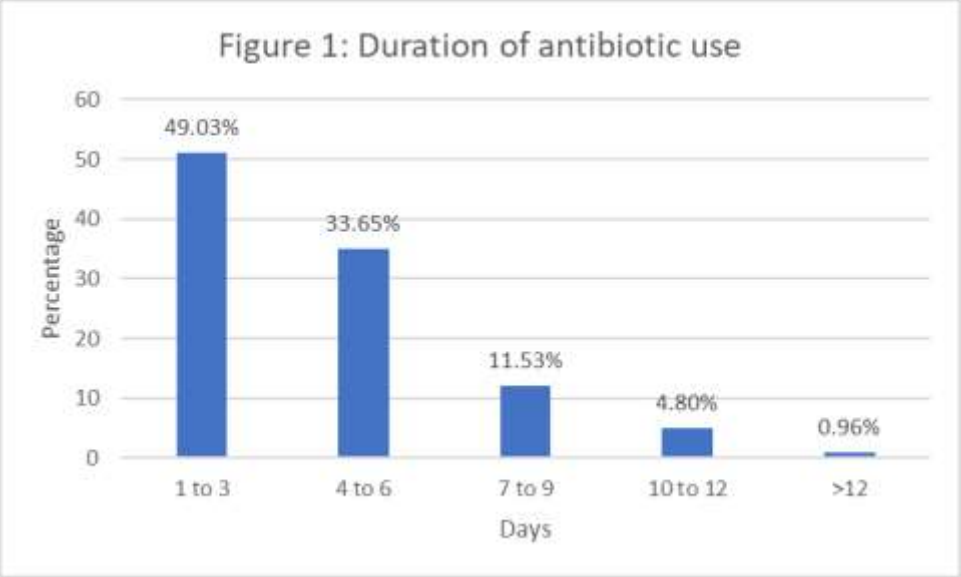

Figure 1: Median duration of antibiotic treatment was 4 days (Inter Quartile Range 1-16).

The association between simultaneous infection status vs disease details is represented in Table 5. Proportion of patients with severe disease was more in patients with a simultaneous infection (63.6%) than those without (20%), p=0.003. Similarly, a significant association was noted between the patient outcome (14 days) and presence of simultaneous infection, with proportion of mortality cases more in those with a simultaneous infection compared with those without (72.7% vs.12.7%), p=<0.001. Longer duration of stay (10-12 and >12) was more commonly noted in those with a simultaneous infection compared with those without (p=0.002).

Table 5: Comparison between COVID 19 patients with simultaneous infections versus no simultaneous infections.

Parameters	**Simultaneous infection Present (n = 11)**	**Simultaneous infection Absent (n = 165)**	**Total 100%**	**p-value**
Severity				
Mild	4 (36.4)	119 (72.1)	123	0.003
Moderate		13 (7.9)	13	
Severe	7 (63.6)	33 (20.0)	40	
Need for ICU				
Yes	6 (54.5)	27 (16.4)	31	0.006
No	5 (45.5)	138 (83.6)	143	
Outcomes at 14 days				
Death	8 (72.7)	21 (12.7)	29	< 0.001
Recovered	1 (9.1)	121 (73.3)	122	
Remains hospitalised	2 (18.2)	23 (13.9)	25	
Presence of co-morbidities				
Yes	11 (100.0)	128 (77.6)	139	0.123
No		37 (22.4)	37	
Total stay in hospital (days)				
1-3	2 (18.2)	59 (35.8)	61	0.002
4-6	1 (9.1)	59 (35.8)	60	
7-9	1 (9.1)	14 (8.5)	15	
10-12	4 (36.4)	9 (5.5)	13	
>12	3 (27.3)	24 (14.5)	27	

Days of stay in ICU	n = 6	n = 27		
1-3	1 (16.7)	12 (44.4)	13	
4-6	1 (16.7)	7 (25.9)	8	0.175
7-9	2 (33.3)	1 (3.7)	3	
10-12	1 (16.7)	2 (7.4)	3	
>12	1 (16.7)	5 (18.5)	6	

Table 6 represents the association between the antibiotic use and patient characteristics, and disease details. Antibiotics were more frequently used in female patients (69%). At the same time 52.3% of male patients received antibiotic, and this difference is significant (p=0.030). Among those patients with a simultaneous infection (n=11), antibiotics were used in 90.9% (n=10), compared with 57% (n=94) among 165 without a simultaneous infection (p=0.029) . It needs to be acknowledged that 4 of the 11 patients had a fungal infection which does not need a treatment with antibiotics.

Table 6: Demographics, severity of illness and outcomes of patients who received antibiotics versus not received.

Parameters	**Antibiotic used (n = 104)**	**Antibiotics Not used (n =72)**	**Total (100%)**	***p*-value**
Age group				0.164
18-30	7 (53.8)	6 (46.1)	13	
31-45	17 (51.5)	16 (48.48)	33	
46-60	17 (45.9)	20 (54)	37	
61-75	36 (66.6)	18 (33.3)	54	
> 75	27 (69.2)	12 (30.7)	39	
Gender				0.030
Male	55 (52.3)	50 (47.6)	105	
Female	49 (69)	22 (30.9)	71	
Severity				0.308
Mild	69 (56)	54 (43.9)	123	
Moderate	10 (76.9)	3 (23)	13	
Severe	25 (62.5)	15 (37.5)	40	
Status of stay in ICU				0.238
Yes	23 (69.69)	10 (30.3)	33	
No	81 (56.64)	62 (43.5)	143	
Length of hospital stay				0.060
1-3	29 (47.5)	32 (52.4)	61	
4-6	37 (61.66)	23 (38.3)	60	
7-9	13 (86.66)	2 (13.33)	15	
10-12	7 (53.8)	6 (46.15)	13	
>12	18 (66.6)	9 (33.3)	27	
Outcomes at 14 days				0.196
Death	21 (72.4)	8 (27.58)	29	
Remains hospitalized	67(54.9)	55 (45)	122	
Recovered	16 (64)	9 (36)	25	
Presence of co-morbidities				0.997
Yes	82 (58.99)	57 (41)	139	
No	22 (59.45)	15 (40.54)	37	

Presence of simultaneous infection				0.029
Yes	10(90.9)	1(9.1)	11	
No	94(57)	71(43.0)	165	

Table 7 shows the association between of the number of antibiotics used and patients', and disease characteristics. A higher antibiotic use (number of antibiotics used) was noticed in those patients with severe disease compared with those with mild or moderate disease; 24%, 10% and 1.4% patients with severe, moderate and mild disease, respectively were treated with 3 antibiotics, p=0.002. Percentage of patients who received 2 or more antibiotics were higher among those patients with simultaneous infection than those without it, p=0.002. With regard to the admission to the ICU, the percentage of patients treated with 2 or more antibiotics was higher comparing to those who were not admitted to the ICU, p=0.03. With regard to the clinical outcome at 14 day, an increased rate of mortality was observed among those receiving 2 or 3 antibiotics, p=0.002.

Table 7: Comparison of the number of antibiotics used with patientdemographics and disease characteristics.

Parameters	**Number of antibiotics used**					**Total (100%)**	***p*- value**
	1 (n = 66)	**2 (n = 28)**	**3 (n = 8)**	**4 (n =1)**	**5 (n = 1)**		
Age group							0.224
18-30	5 (71.4)	2 (28.57)				7	
31-45	13 (76.47)	3 (17.6)	1 (12.5)			17	
46-60	7 (41.17)	10 (58.8)				17	
61-75	24 (66.66)	8 (22.2)	2 (5.55)	1 (2.77)	1 (2.77)	36	
> 75	17 (62.9)	5 (18.5)	5 (18.5)			27	
Gender							0.375
Male	33 (60)	16 (29)	6 (10.9)			55	
Female	33 (67.34)	12 (24.4)	2 (4.08)	1 (2,94)	1 (2.94)	49	
Severity							0.002
Mild	49 (71)	19 (27.5)	1 (1.4)			69	
Moderate	8 (80)	1 (10)	1 (10)			10	
Severe	9 (36)	8 (32)	6 (24)	1 (4)	1 (4)	25	
Status of stay in ICU							0.03
Yes	10 (43.4)	8 (34.7)	3 (13)	1 (4.3)	1 (4.3)	23	
No	56 (69)	20 (24.7)	5 (6.17)			81	
Total stay in hospital							0.101
1-3	18 (62)	9 (31)	2 (6.89)			29	
4-6	28 (75.6)	8 (21.6)	1 (2.7)			37	
7-9	9 (69.2)	2 (7.1)	2 (25.0)			13	
10-12	2 (3)	5 (17.9)				7	
>12	9 (50)	4 (22.2)	3 (16.6)	1 (5.55)	1 (5.55)	18	
Outcomes at 14 days							0.002
Death	8 (38)	8 (38)	4 (19)	1 (4.8)		21	
Remains hospitalised	50 (74.6)	16 (23.8)	1 (1.49)			67	
Recovered	8 (50)	4 (22.2)	3 (16.6)		1 (6.25)	16	
Presence of co-morbidities							0.386
Yes	53 (64.6)	22 (78.6)	6 (75.0)	1 (100.0)		82	
No	13 (59.5)	6 (27.2)	2 (9.8)		1 (100.0)	22	
Presence of Simultaneous infection						10 94	0.002
Yes	2(20)	5(50)	2(20)	1(10)	0(.0)		

No	64(68.1)	23(24.5)	6(6.4)	0(.0)	1(1.1)

Discussion

Major finding in the study was that in vast majority of the patients who received antibiotics, there was no reported bacterial co-infection and accordingly no clear indication for its use. Patient demographics and disease details.

In the present study, the highest percentage of patients (30.7%) were between the age of 61 to 75 years. This could be explained that more severe form of disease and need for hospitalization due to COVID-19 during the omicron wave was more common among the elderly as a general trend. Similarly in the study conducted in China by Wei et al, severe cases of Omicron variant COVID-19 tended to be older. [14] In a study conducted in Japan comparing Omicron and pre-Omicron period, patients with COVID-19 during the Omicron period were older and had more comorbidities.[15]

In our study most of the hospitalized patients had mild disease (69.9%) followed by severe cases (22.7%). This was expected as the present study was based on Omicron variant and infection caused by this variant is relatively milder.[16,17]Thought all of the admitted cases from March 2020 until November 2021 were moderate to severe COVID 19 patients, with the emergence of omicron variant globally and in Oman from December 2021 until February 2022, most of the cases presented to Royal Hospital were mild cases. In addition, during this period a number of patients were admitted for other reasons but found to be positive by screening and tend to have mild symptoms. The admission of mild cases may have been due to coinfections necessitating antibiotic treatment or underlying health conditions (co-morbidities) and daily reassessment to prevent complications or deterioration of their condition. Murakami et al as well reported that more than the severity of the illness by SARS-CoV-2, but coinfection or deterioration of an underlying disease had a significant effect on hospitalization during the Omicron period. [15]. In the present study, 69% of the patients recovered from the disease while 17% died according to the outcome assessed at 14 days. Relatively, this mortality rate could be considered high, relating to the fact that COVID-19 by Omicron is expected to be less severe and less likely to cause mortality compared to certain other strains of SARS-CoV-2 , however, a high number of patients in this cohort were old age and had comorbidities. In the study conducted in Iran during Omicron wave, the death rate among hospitalized patients with confirmed BA.5 infection was 6.25%. [18] In another study reported from a hospital in California, USA, adults hospitalized with SARS-CoV-2 infection during Omicron predominance, was associated with lower likelihood of intensive care unit admission. Authors reported that compared with patients during the period of Delta predominance, Omicron-period patients had less severe illness, largely driven by an increased proportion who were fully vaccinated.[19]

In our cohort, only 11 patients (6.3%) had simultaneous infection among which the confirmed bacterial infection was only in 7 patients (4%). Though an infection was suspected in a good number of cases, a confirmed simultaneous infection was documented only in a minor percentage of patients. Similarly, in Germany, relevant pathogens were detected in 10 cases (7.1%) out of 140 COVID-19 patients which is similar to the our study.[20] In contrary in another study conducted in the USA the percentage of bacterial coinfection was higher (19%).[21]In a study conducted in Iran, a higher percentage (14.4%) of confirmed bacterial co infection was reported.[22] On the other hand, in another study conducted in Pakistan, relatively low percentage (1.4%) of secondary bacterial infection or co-infection was identified.[23] A very high percentage of coinfections in Omicron period than in the pre-Omicron period (44.4% versus 0.8%) were noticed in the study conducted in Japan.[15] In the recently published global study conducted by WHO from 01/01/2020-30/03/2023 using data from 592,898 patients in 65 countries, suspected co-infections were reported in 7.9% of patients.[24]

In the present study, *E. coli* was isolated in 2 (18.2%) of the patients with a simultaneous infection while one (9.1%) patient had *Staphylococcus aureus* infection. Presence of *E. coli* cases with simultaneous infection could be related to the urinary source being the second most common infection after septic shock in the present study. In the international study conducted by Papst et al, the percentage of *E.coli* was almost near to the present study as the number of patients that have *E.coli* are 17.5%.[25] In the study conducted in USA as well, the most common organism was *E.coli* (26%) which is higher than the present study.[21] Candida *spps.* were isolated in 4 patients, indicating probably superinfections rather than co infections.

The proportion of patients who received antibiotics in this study is 59%which is higher than the values (43.4%) reported among pediatric patients hospitalized with COVID-19 during the Omicron wave at a referral hospital in Peru. [26] A study conducted in Hongkong demonstrated a high prescription rate of antibacterial drugs among

hospitalized patients infected in the local community in Hong Kong. [27] In the global study conducted by WHO covering all waves of COVID-19 infection from 01/01/2020-30/03/2023, antibiotic use showed vast inter-regional variability ranging from 83.0% in the Eastern Mediterranean Region (EMR) to 32.8% in Western Pacific Region. [24] The rate of antibiotic use among COVID-19 patients in the period prior to Omicron wave in studies conducted in USA, Jordan, Ireland and Pakistan were reported as 67%, 69%, 78.4%, and 93.7%, respectively. [21, 23, 28, 29]

In this study, the vast majority the patients received an antibiotic despite that only 11% were having a confirmed simultaneous infection. The overuse of antibiotics could be explained by the fact that COVID-19 patients can be rather be very sick at the admission and sometimes it almost impossible to rule out an infection. The start of the empirical antibiotic was followed by daily assessment of the patients by the antimicrobial stewardship team in the hospital , and in most cases antibiotics were stopped within 72 hours if microbiological cultures were negative . The use of antibiotics in our study has been higher than a study by O Kelly et al. where 66.4% of the patients were prescribed antibiotics empirically for pneumonia.[21] However, similar to our study, in the study from Pakistan, 96.3% of patients were prescribed antibiotics empirically on presentation .[23]

In the current study, the most commonly used antibiotics among those who received them were systemic that included: ceftriaxone, piperacillin and tazobactam (45.2%) , vancomycin (21.2%) and meropenem (15.4%). Oral doxycycline and azithromycin were the least commonly used antibiotics (0.96%). Similarly, the most commonly prescribed antibiotic in reports from both the USA and Bangladesh was ceftriaxone.[21,30] While azithromycin was the least used antibiotic in our study, in the study conducted in Oman by Khamis et al,[11] azithromycin was among the most commonly used antibiotic (71%). This could be explained by the reason that the mentioned study was conducted during the wave by Wuhan virus, where in azithromycin was a commonly prescribed agent that later was disproved by several studies. . In the USA, vancomycin and azithromycin were used more often comparing to our study. [21] In the study conducted in Dublin, the most common antibiotics prescribed were piperacillinand tazobactam, ceftriaxone and co-amoxiclav.[29] Additionally, in the study conducted in Jordan, fluoroquinolone (31.9%) and macrolide (25.0%) followed by third generation cephalosporin (17.6%) were used.[28]These differences in the antibiotics used in various reports which widely varied from the present study could be explained by the time of conduct of these studies, different recommendations in the individual countries, availability and local resistance patterns. In our study, almost half of the patients received antibiotics for 1 to 3 days and 33.5% for 4 to 6 days. In the study conducted in Jordan, only 17.5% of patients were on antibiotics for less than 3 days..[28] Early discontinuation of antibiotics because of absence of positive microbial culture might have a positive effect in reducing the additional risk of antibiotic resistance.

In the present study it was noticed that presence of simultaneous infection had a negative influence on severity of the disease, mortality and duration of hospital stay. Similarly, in the study conducted in China, compared to the non-severe patients, the proportion of patients who had bacterial co-infections was significantly higher in the severe and critical Omicron groups. [14]

Statistically significant difference was observed between the status of antibiotic use and two parameters; gender and presence of simultaneous infection. Antibiotics were more frequently used among female patients compared with male patients. In those patients with a simultaneous infection, antibiotics were used in 90.9% of patients compared with 57% in those without a simultaneous infection. The finding that female patients more frequently received antibiotics could be related to the difference in the severity of disease based on gender, but only further analysis could give the proper explanation. The patients with a simultaneous infection were sicker and had a more severe disease which explains the higher percentage of antibiotic use among these group of patients. Unlike our study where no significant relationship was noticed between status of antibiotics prescribed and outcome, in the study conducted in Jordan, non-survivors were more likely to have been prescribed antibiotics than survivors (93.1% vs. 65.2%).[28]

A significant association was noted between number of antibiotics used and severity of disease, presence of simultaneous infection, admission to the ICU, and patient outcome at 14 days. A higher number of antibiotics were used among those patients with a severe disease compared with those with mild or moderate disease. This could be explained with the severity of the disease and presence of a simultaneous infection. Patients with more severe disease and/or comorbidities tend to be prescribed multiple antibiotics and often are treated longer. Furthermore, the prolonged hospital stay increases the possibility of acquiring hospital infection, hence more antibiotics are prescribed. In the scoping review conducted by Cong et al, the antibiotic prescribing rate for severe COVID-19 patients was 75.3% and 48.3% compared with 75.1% and 15.5% for mild and moderate patients during results from two study periods in the pre-Omicron phase.[31]

Though, no significantly higher proportion of death was noticed among patients who received antibiotics compared with those who did not, severe disease and death as an outcome was more commonly observed among patients who received 2 or more antibiotics. One potential explanation could be that proportion of severe cases and death as the outcome was more among patients with simultaneous infection and these patients might have received multiple antibiotics. At the same time, the influence of the use of multiple antibiotics on the negative outcome among patients cannot be ruled out. In the present study, single antibiotics were more likely to have been used in patients who recovered than who died (50.0% vs. 38%) . This could be explained by considering that these patients might had milder disease and they recovered faster. On the other hand, in the study conducted in Jordan, non-survivors were more likely to have been prescribed single antibiotics compared to survivors (55.2% vs. 34.8%).[28] In the global study reported by WHO, a sensitivity analysis focusing on patients without suspected or confirmed bacterial infection showed nearly twice the risk of death among mild/moderate patients receiving empiric therapy compared to those not receiving antibiotics and a 16% higher risk among those severe/critical patients.[2]

The study has several limitations. This is a single centre study hence the results cannot be generalized as the pattern of the antibiotic usage throughout the country, although Royal Hospital was in the forefront in managing COVID-19 patients and preparing national recommendations for treatment of COVID-19 patients. The study is a retrospective in nature which contributes to the limitations of the obtained data. The present study is limited to the patients treated during Omicron variant wave and the number of published studies about the antibiotic use during infection with Omicron variant is limited So the adequate comparison in this group of patients is hard to be made.

Conclusion

The finding that in vast majority of the patients who received antibiotics, there was no reported bacterial co-infection and accordingly no clear indication for its use is not encouraging and requires inquisition. Though there was no clear evidence to state that status of use of antibiotics influenced the clinical outcome among the patients, proportion of death were higher among those receiving multiple antibiotics..

Though the COVID-19 pandemic was an unprecedented emergency situation and treatment recommendations varied during different periods, and availability of consistent and reliable information was lacking, there are few recommendations that could be derived from the findings of the study. Over and unnecessary use of antibiotics was reported globally, it is imperative that a more in-depth evaluation behind the reasons for the use of antibiotics so widely in cases with no confirmed bacterial simultaneous infections should be done locally to be prepared for such situations in future. Ensuring an active antimicrobial stewardship in place even during such unprecedented situations could definitely promote safe and effective use of antimicrobials. Detailed evaluation, education and development of policies is crucial to avoid such practices in future instances.

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