

Original Article



OPEN ACCESS

Received: Feb 3, 2022

Accepted: Apr 26, 2022

Published online: Jun 10, 2022

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Funding

None.

Conflict of Interest

No conflict of interest.

Author Contributions

Conceptualization: WAG-DL, JAB. Data curation: WAG-DL. Formal analysis: WAG-DL. Investigation: WAG-DL. Methodology: WAG-DL, JAB. Project administration: WAG-DL.

Prevalence of Empiric Antibacterial Therapy, Community-Acquired Bacterial Superinfection, and Antibiotic-Associated Adverse Reactions among Patients with COVID-19 Pneumonia Admitted in Makati Medical Center from March 2020 to March 2021

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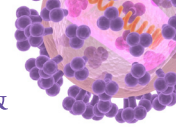
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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus which was first discovered in Wuhan, China. Being a viral illness, antibacterial agents theoretically have no role in patients with pure COVID-19 infection. However, like any viral illness, concomitant bacterial infection may occur. The dilemma of starting an antibacterial agent in a COVID-19 patient remains a debate since the use of antibacterial agents may pose a risk of developing antibiotic-associated adverse events such as the emergence of drug-resistant pathogens and other antibiotic-associated drug toxicity. The primary objective of the study is to determine the amount of empiric antibacterial prescription done by physicians among admitted patients with COVID-19 infection as well as the trend of antibiotic prescription by physicians during the past 12 months of the COVID-19 pandemic. The secondary objective was to determine and quantify antibiotic-associated adverse effects.

Materials and Methods: This is a retrospective cohort study wherein charts of patients admitted for COVID-19 last March 2020 to March 2021 were reviewed and analyzed. Empiric antibiotic prescription during the first 48 hours of admission was noted as well as the proportion of concomitant bacterial infections. Development of antibiotic-associated adverse events such as the development of the multidrug-resistant organism and fungal infections, *Clostridioides difficile* and/or gastrointestinal side effects, and hypersensitivity reactions were also noted.

Results: Results showed that among the 895 patients with COVID-19 admitted, 533 (59.6%) patients were started antibiotics during the first 48 hours of admission. Among those patients who are started with antibacterial therapy during the first 48 hours of admission, 60 (15.3%) patients had bacterial coinfection. The prevalence of antibiotic-associated adverse events was 46.9%, the most common of which was gastrointestinal reactions. The overall mortality rate of the patients given antibiotics was 18.8%. The median length of hospital stay was 11 days.



Resources: WAG-DL. Software: WAG-DL.
 Supervision: JAB. Validation: WAG-DL.
 Visualization: WAG-DL. Writing - original draft:
 WAG-DL, JAB. Writing - review & editing:
 WAG-DL, JAB.

Conclusion: Community-acquired bacterial infections in COVID-19 patients admitted during the study period were low while empiric antibiotic prescription was high especially during the first few months of the pandemic, especially during the surge. Antibiotic-related adverse effects were high. There was a noted decreasing trend of antibiotic prescription during the latter part of the pandemic when new developments in COVID-19 treatment were discovered. All in all, routine antibacterial prescription in patients with COVID-19 is not recommended given the real-world data in this study.

Keywords: Antimicrobial stewardship; COVID-19; Antibiotic resistance

INTRODUCTION

In December 2019, an outbreak of a new viral disease was first seen in the city of Wuhan, China. The causative agent was subsequently identified as a new strain of coronavirus that was later named, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). According to the World Health Organization, as of April 20, 2022, the number of confirmed cases around the world afflicted with coronavirus disease 2019 (COVID-19) reached 504,079,039 including 6,204,155 deaths and 575,667 new cases [1].

The clinical presentation of COVID-19 is varied and can range from mild flu-like symptoms to a more severe presentation of pneumonia and acute respiratory distress syndrome [2-4]. Being a viral illness, antibacterial agents have no benefit in patients afflicted with purely COVID-19 infection. On the other hand, like any other viral illness, a COVID-19 patient also has a risk to develop a concomitant bacterial infection. Data on bacterial coinfections among COVID-19 patients are quite limited and usually range from 3.0 – 30.0% [5, 6] Similar to other studies, it was noted that many patients with COVID-19 infection were often started with early empiric antibiotic therapy despite the lack of evidence of a bacterial superinfection [6, 7]. This was particularly notable during the early part of the pandemic wherein the disease was quite new and no established treatment was present. The increased use of unnecessary antibiotic therapy in purely COVID-19 infection can pose the development of antibiotic-associated adverse effects such as the emergence of resistant bacterial strains and other drug reactions [7].

This study aimed to document the amount and the trend of antibiotic prescription by doctors for hospitalized COVID-19 patients for the past 12 months, as well as to determine the prevalence of community-acquired bacterial co-infection among patients with SARS-CoV-2 infections. This study also aimed to determine the prevalence of antibiotic-associated adverse effects, such as multidrug-resistant bacterial infections, fungal infections, allergic or hypersensitivity reactions, gastrointestinal side effects, and *Clostridioides difficile* infections in the same population as well as the percentage of patients who received and did not receive antibiotic who survived/died and their length of hospitalization.

MATERIALS AND METHODS

1. Data collection

A retrospective cohort study was done wherein medical records of confirmed COVID-19 patients admitted in Makati Medical Center from March 1, 2020, to March 31, 2021, were analyzed. All adult patients aged 18 years old and above with at least one positive COVID-19 polymerase chain

reaction (PCR) results within the first seven days of admission were eligible for data analysis. Excluded subjects include those who were below 18 years old, discharged against medical advice in the emergency room, transferred to another institution, those who were transferred from another hospital, and those who opted to undergo home quarantine. Patients with previous hospitalization within the previous 90 days as well as those who have antibiotic use within 90 days prior to the present admission were also be excluded. All data that will be used in this research was collected from the medical charts of the patients who are admitted with COVID-19 infection. The data that were collected include the patient's demographics, comorbidities, antibiotics prescribed, laboratory parameters, culture results, and radiologic imaging results. The severity of the COVID-19 infection on presentation was also noted. A total of 1,705 charts were reviewed and a minimum of 346 sample size was computed using an online software OpenEpi version 3 (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06, accessed 2021/06/03.). Frequency of the antibiotic prescription of doctors during the first 2 days of the hospitalization was noted. Antibiotics that were started on the third day of hospitalization and beyond were not considered since the antibiotics may have been started to target a nosocomial infection. Frequency of community-acquired bacterial infections was also noted. Bacterial co-infections were identified by having positive culture results (blood, sputum, endotracheal aspirate, urine, pleural, peritoneal or wound cultures or other tests that would denote a bacterial infection such as *Mycoplasma* PCR, *Legionella* PCR, or pneumonia panel - all taken within the first 48 hours of admission. The white blood cell count, procalcitonin, chest X-ray findings, and urinalysis were also noted. Bacterial co-infections were considered community-acquired if the tests were taken during the first 2 days of admission. To rule out colonizers and contamination as possible causes of positive cultures, all patients with positive bacterial cultures that were included in the data analysis were the ones who were treated as having a true bacterial infection based on the clinical status of the patient during that time. This was further supported by laboratory evidence of bacterial infections such as increased procalcitonin and increased white blood cell count. Development of any antibiotic associated adverse effects, including the development of multidrug-resistant bacterial infection which was defined as the presence of a non-susceptible bacteria to at least one antibiotic in three or more antimicrobial categories, development of extensively drug-resistant pathogen defined as non-susceptibility to at least one antibiotic in all but two or fewer antibiotic categories and pan drug-resistant isolate defined as non-susceptibility to all antibiotic agents [5], development of *C. difficile* infection, allergic and/or hypersensitivity reactions, and gastrointestinal reactions such as diarrhea, nausea, vomiting or abdominal pain, which were potential complications of antibiotic use were also noted. No further patient follow-up was done after discharge since this was a retrospective study. Lastly, the total antibiotic prescription trend from March 2020 to March 2021 was also determined and analyzed.

2. Ethics statement

This study was approved by the hospital's institution review board last May 31, 2021 with designated protocol number MMCIRB 2021-021. No informed consent from any patient was obtained since this study used chart review in obtaining data. Patient confidentiality was strictly upheld for the whole duration of this study.

3. Statistical analysis

Descriptive statistics were used to check the general features and clinical characteristics of the patients. Chi-square was used to check for the correlation of the baseline characteristics of the patients. Frequency and proportion were used for categorical variables. Shapiro-

Wilk test was used to check the normality distribution of continuous variables. Continuous quantitative data that met the normality assumption was summarized using mean and standard deviation (SD), while those that do not were described using median and range. All valid data were included in the analysis. 95% confidence intervals (CI) of the proportion were reported for point estimates. Missing variables were neither replaced nor estimated. STATA 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

RESULTS

Figure 1 shows that of 895 patients with a positive RT-PCR test within the study period, empiric antibiotic therapy was initiated in 533 (59.6% [57.59 - 61.51]) patients. **Table 1** shows the baseline characteristics and demographics of the participants. It was noted that there was no significant correlation in terms of gender when starting antibiotics however in other characteristics there is a significant correlation in terms of starting antibiotics. Elderly patients, those with comorbidities, and those patients with severe and critical COVID-19 on admission were more likely to be given antibiotics.

Table 2 shows that among those with bacterial cultures taken, empiric antibiotics were initiated in 43.8% (41.83 - 45.75), while in those without cultures, empiric antibiotics were initiated in 15.8% (13.79 - 17.71). **Figure 2** shows that the most prescribed antimicrobials were azithromycin, piperacillin-tazobactam, and ceftriaxone.

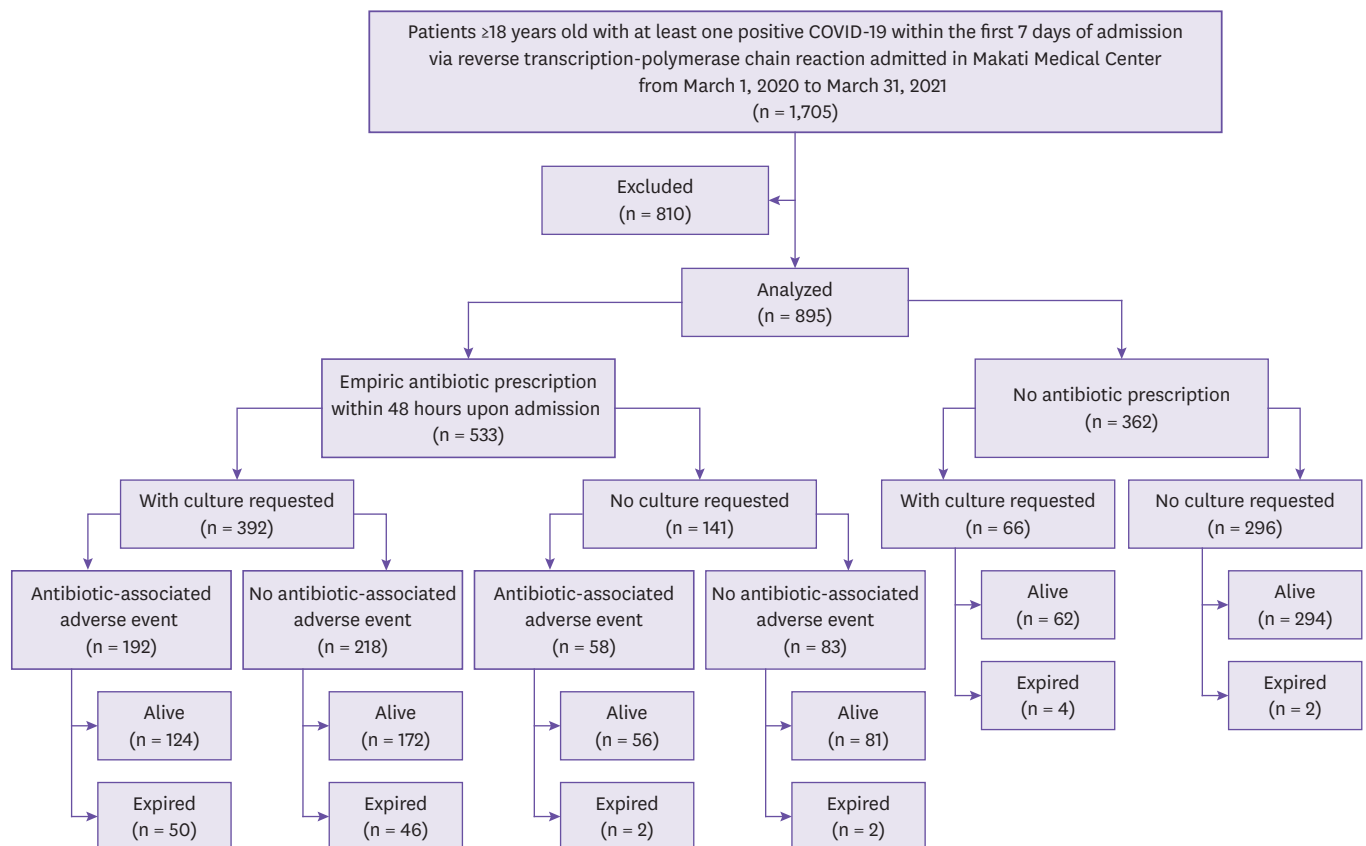


Figure 1. Flowchart of patients.

Table 1. Baseline characteristics and demographics of the participants

	With empiric antibiotic (n = 533)	No antibiotic prescription (n = 362)	P-value
Age			<0.001
<65	323 (61.0%)	288 (79.0%)	
65 - 80	198 (37.0%)	61 (17.0%)	
>80	12 (2.0%)	13 (4.0%)	
Gender			0.007
Male	316 (59.0%)	186 (51.0%)	
Female	217 (41.0%)	176 (49.0%)	
Coexisting comorbidities			<0.001
No comorbidities	143 (27.0%)	169 (47.0%)	
Hypertension	306 (57.0%)	146 (40.0%)	
Diabetes mellitus	209 (39.0%)	89 (25.0%)	
Chronic obstructive pulmonary disease	18 (3.0%)	6 (2.0%)	
Asthma	47 (9.0%)	26 (7.0%)	
Chronic kidney disease	65 (12.0%)	15 (4.0%)	
Cancer	21 (4.0%)	9 (2.0%)	
Congestive heart failure	32 (6.0%)	11 (3.0%)	
COVID-19 Severity on admission			<0.001
Mild	45 (8.0%)	126 (35.0%)	
Moderate	140 (26.0%)	160 (44.0%)	
Severe	142 (27.0%)	59 (16.0%)	
Critical	206 (39.0%)	17 (5.0%)	

COVID-19, coronavirus disease 2019.

Table 2. Frequency of early empiric antibiotic prescription among admitted adult COVID-19 patients (n = 895)

	Empiric antibiotic use	
	Frequency	Proportion [95% CI]
Overall	533	59.6 [57.59 - 61.51]
With bacterial culture	392	43.8 [41.83 - 45.75]
Without bacterial culture	141	15.8 [13.79 - 17.71]

COVID-19, coronavirus disease 2019; CI, confidence interval.

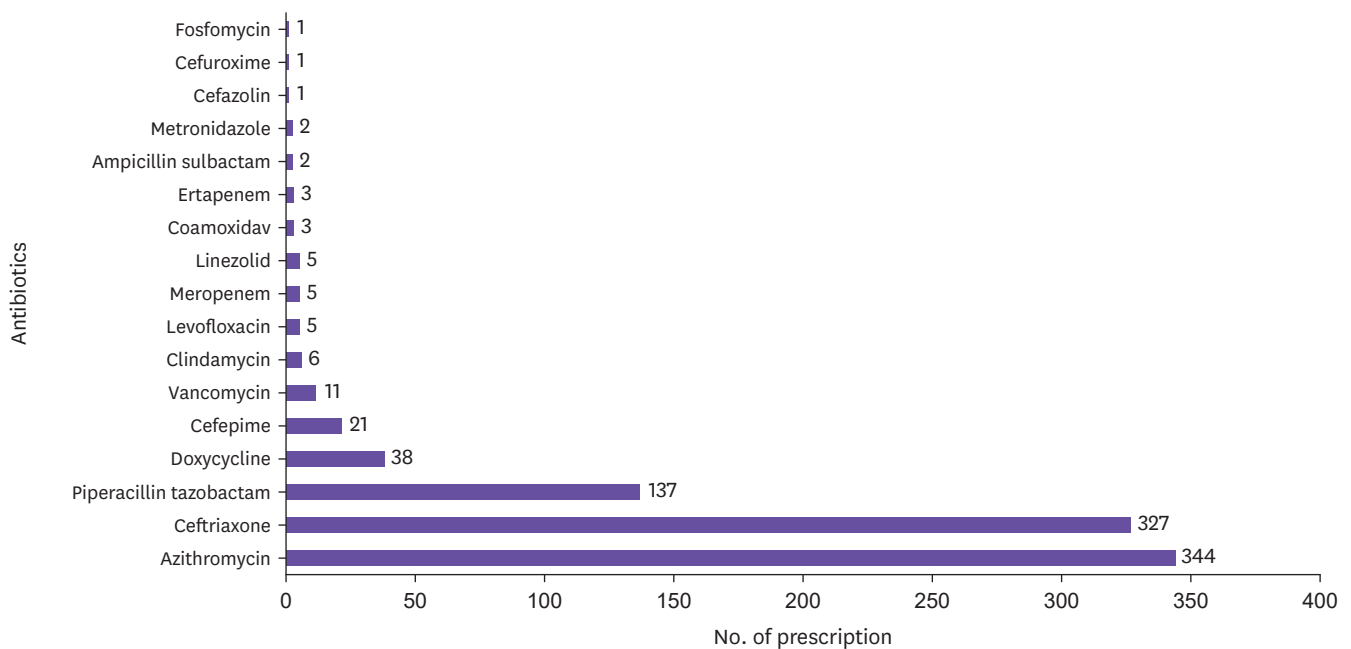


Figure 2. Empiric antibiotics given to admitted coronavirus disease 2019 patients.

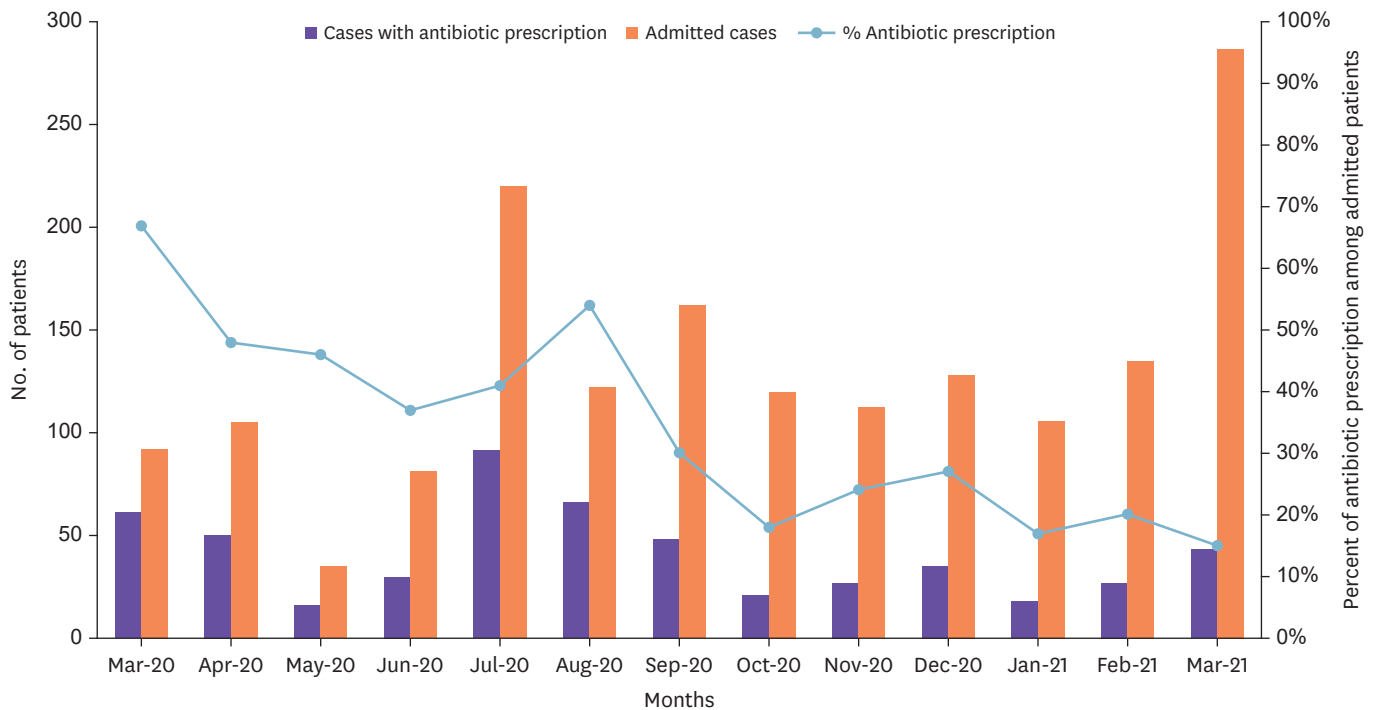
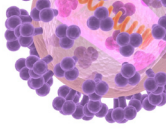


Figure 3. Monthly rates (in absolute counts and percentage) of empiric antibiotic prescription among admitted coronavirus disease 2019 (COVID-19) adults from March 2020 – March 2021 in Makati Medical Center.

Figure 3 depicts the two peaks in the empiric therapy prescription rates were seen during the study period: one in March 2020, at the beginning of the pandemic; and another in August 2020. A downward trend on the monthly rates of prescription cases was only seen in September 2020 onwards.

Table 3 portrays that among patients who had bacterial culture, bacterial coinfection was observed in 63 patients, or 13.8% (95% CI: 10.73 - 17.25). Among patients who had antibiotic prescriptions within 48 hours upon admission, bacterial coinfection was seen in 60 patients, or 15.3% [95% CI: 11.89 - 19.26%]. Among patients who did not have an antibiotic prescription, bacterial coinfection was detected in three patients, or 4.6% (95% CI: 0.95 - 12.71). **Table 4** shows that the occurrence of any antibiotic-related adverse event was 46.9% (95% CI: 42.60 - 51.24), the most common of which was gastrointestinal reactions.

1. Mortality

Table 5 shows that among patients who were considered to require empiric antibiotics, the overall mortality rate was 18.8%. Mortality was at 26.7% for culture positive patients and 24.1% for culture negative patients, and 2.8% for those in whom cultures were not necessary to be taken. Meanwhile, among patients in whom there were antibiotics prescribed, the

Table 3. Frequency of bacterial coinfection identified within 48 hours of admission

	N	Bacterial coinfection identified within 48 hours of admission	
		Frequency	Proportion [95% CI]
Overall	458	63	13.8 [10.73 - 17.25]
With antibiotic prescription within 48 hours upon admission	392	60	15.3 [11.89 - 19.26]
No antibiotic prescription	66	3	4.6 [0.95 - 12.71]

CI, confidence interval.

Table 4. Frequency of antibiotic-associated adverse events among adult COVID-19 patients with empiric antibiotic prescription during the first 48 hours upon admission (n = 533)

Antibiotic-associated adverse event	Frequency	Proportion [95% CI]
Any event	250	46.9 [42.60 - 51.24]
Gastrointestinal reaction	212	39.8 [35.59 - 44.07]
Fungal infection	68	12.8 [10.04 - 15.89]
Multidrug resistant infection	46	8.6 [6.39 - 11.34]
<i>Clostridioides difficile</i> infection	8	1.5 [0.65 - 2.94]
Allergic or hypersensitivity reaction	3	0.6 [0.12 - 1.64]

COVID-19, coronavirus disease 2019; CI, confidence interval.

Table 5. Patient outcomes among admitted COVID-19 patients

	With empiric antibiotic (n = 533)	No antibiotic prescription (n = 362)	P-value
Mortality (number, rate [95% CI])			
Overall	100; 18.8 [15.53 - 22.34]	6; 1.7 [0.61 - 3.57]	<0.001
Culture positive	16; 26.7 [16.07 - 39.66]	1; 33.3 [0.84 - 90.57]	0.999
Culture negative	80; 24.1 [19.59 - 29.07]	3; 4.8 [0.99 - 13.29]	<0.001
Culture not given	4; 2.8 [0.78 - 7.10]	2; 0.7 [0.08 - 2.42]	0.088
Length of hospital stay, median days (range)			
Overall	11 (0 - 181)	6 (1 - 67)	<0.001
Culture positive	14.5 (2 - 105)	16 (4 - 22)	0.821
Culture negative	12 (0 - 181)	6 (2 - 34)	<0.001
Culture not given	9 (2 - 41)	6 (1 - 67)	<0.001

COVID-19, coronavirus disease 2019; CI, confidence interval.

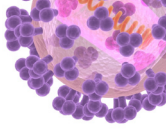
overall mortality was at 1.7% but was at 33.3% for the culture positive patients. For culture negative patients, it was at 4.8%, while for those without cultures, it was 0.7%.

2. Length of hospital stay

Similarly, **Table 5** portrays that the median length of hospital stay was at 11 days (ranging from 0 - 181) for those who required empiric antibiotics and at six days (ranging from 1 - 67) for those who did not require antibiotic prescription. Culture positive patients had a median hospital stay of 14.5 days (maximum 105 days) for those with antibiotics and 16 days for those without antibiotics. Culture negative patients stayed for a median of 12 days among those given antibiotics and six days among those not given antibiotics. For patients without cultures, the length of hospital stay was 9 days (maximum 41 days) for those who received antibiotics and 6 days for those who did not receive antibiotics (maximum of 67 days).

DISCUSSION

In this study, it was noted that there is a high prevalence of empiric antibiotic prescription among COVID-19 patients who were seen and admitted in this institution especially in the early part of the pandemic and during the second surge in congruence with the rise of COVID-19 cases in our country. This finding is not surprising since, in the early days of the pandemic, COVID-19 pneumonia may manifest like bacterial pneumonia. Aside from this, there is limited knowledge in the treatment modalities used in the management of COVID-19 patients in the early part of the pandemic hence several treatment modalities were tested. This finding is also consistent with the findings of the study done by Rawson et al wherein they noted 72.0% of patients diagnosed with COVID-19 were also given antibiotic therapy [8].



Azithromycin is the most common antibiotic prescribed among patients with COVID-19. This is followed by ceftriaxone and piperacillin-tazobactam. This trend was consistent throughout the study period even though azithromycin was postulated to be a possible treatment for COVID-19 during the early part of the pandemic. It is also likely that the initial papers pointing to the efficacy of azithromycin stuck to clinical practice despite evidence later on that it was not efficacious for COVID-19. These antibiotics were the common antimicrobials used in patients with bacterial pneumonia because of their excellent coverage of the common causative agents of bacterial pneumonia. This is somewhat similar to a study done by Calderon-Plaza et al., wherein Beta-lactams were one of the most prescribed antibiotics in patients with COVID-19 [9]. However, it must be noted that 4 out of the top 10 most commonly used antibiotics have anti-Pseudomonal coverage. This may denote overuse of antibiotics since the patients who have a risk to develop pseudomonas infection such as outpatient use of antibiotics, previously admitted for the past 3 months, and those who were transferred from another institution for continuity of care were already excluded prior to the analysis of data.

Despite the high antibiotic prescription rates noted in this study, only 15.3% of the patients given antibiotics have bacterial coinfection. A metanalysis was done by Langford et al, which showed that only 3.5% of COVID-19 patients have primary bacterial co-infection. However, despite having a low rate of bacterial coinfections, 70.0% of the patients have received empiric antibiotic treatment [10].

It is recognized that inappropriate use of antibiotics is hazardous and has its own risks. Patients with pure COVID-19 infection are exposed to its toxic effects and may have an increased risk of acquiring complications despite no evidence of benefit in this subset of patients [10]. In this study, 46.9% of the patients were noted to have adverse events from antibiotics, most common of which were gastrointestinal reactions such as diarrhea, nausea, and abdominal pain. 12.8% and 8.6% of patients developed fungal and drug-resistant infections, respectively. The effect in mortality of those culture-negative patients who were given antibiotics was significant. Also, increased hospital days were noted in those given antibiotics. Discharge criteria were generally the same for the two groups, particularly during the time periods when they were admitted. The only difference was that during the first surge, all patients were generally discharged longer as compared to the later surges, but there were no intergroup differences between those who were given empiric antibiotics and those who were not given antibiotics per surge time period.

In conclusion, prevalence of community-acquired bacterial infections in COVID-19 patients admitted during the study period was low while the prevalence of empiric antibiotic prescription was high especially during the early months of the pandemic and during the surge of COVID-19 cases in the community. Antibiotic-related adverse effects were high. There was a noted decreasing trend of antibiotic prescription during the latter part of the pandemic when new developments in COVID-19 treatment were discovered. All in all, routine antibiotic prescription in patients with COVID-19 is not recommended given the real-world data in this study.

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