Observational Study on Secondary Bacterial Infection and the Use of Antibiotics in COVID-19 Patients Treated in a Tertiary Referral Hospital

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ABSTRACT

***Background*:** *Data on secondary bacterial infection in patients with COVID-19 in Indonesia are still limited, while the use of empirical antibiotics continues to increase. This study aims to determine the secondary bacterial infection rate in hospitalized COVID-19 patients and factors related to secondary bacterial infection.* ***Methods*:** *This is a retrospective cohort study on hospitalized COVID-19 patients undergoing treatment at Cipto Mangunkusumo Hospital from March 2020 to September 2020. Secondary bacterial infection is defined as the identification of a bacterial pathogen from a microbiological examination.* ***Results*:** *From a total of 255 subjects, secondary infection was identified in 14.5%. Predictors of secondary infection were early symptoms of shortness of breath (OR 5.31, 95% CI 1.3 – 21.5), decreased consciousness (OR 4.81, 95% CI 1.77 – 13.0), length of stay > 12 days (OR 8.2, 95% CI 2.9 – 23.3), and central venous catheter placement (OR 3.0, 95% CI 1.1 – 8.0) The most common pathogen of secondary bacterial infection is Acinetobacter sp. (n=9; 28%). Empirical antibiotics were administered to 82.4% of subjects with predominant use of macrolides (n=141; 32.4%).* ***Conclusion*:** *The secondary bacterial infection rate in COVID-19 was 14.5% and is associated with dyspnea, decreased consciousness, length of stay >12 days, and central venous catheter placement. The use of antibiotics in COVID-19 reaches 82.4% and requires special attention to prevent the occurrence of antibiotic resistance.*

Keywords: *COVID-19, secondary bacterial infection, antibiotics, antibiotic stewardship.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory infection with high morbidity and mortality worldwide. This disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has a wide spectrum of diseases from asymptomatic to severe pneumonia resulting in acute respiratory failure and death.[1,2] By 2022, there have been more than 300 million cases and 5 million cumulative deaths due to COVID-19 globally.[3]

Several studies have reported bacterial co-infection and secondary bacterial infection in patients with COVID-19. Langford et al[4] reported that 3.5% of COVID-19 patients had bacterial co-infection, and 14.3% had secondary bacterial infection. Another study on severe and critical COVID-19 also reported a high incidence of bacterial co-infection prevalence of up to 20% of total cases.[5] With the low prevalence of bacterial co-infection and secondary bacterial infection, however, studies showed that more than 70%

of COVID-19 patients who were hospitalized received antibiotics. This excessive use of antibiotics must be monitored closely because excessive and irrational use of antibiotics will affect the normal flora in the body and increase bacterial resistance.[4,6]

This study aims to provide an overview of the incidence of co-infection and secondary infection as well as the causative pathogen in COVID-19 patients. In addition, this study also assessed the predicting factors for the presence of secondary infection in COVID-19 patients undergoing treatment.

METHODS

Study Design and Participant

This retrospective cohort study collected data from medical records of COVID-19 patients who were hospitalized at Cipto Mangunkusumo Hospital. COVID-19 was confirmed by the reverse transcriptase-polymerase chain reaction (RT-PCR) method. Data on confirmed COVID-19 adult patients were collected consecutively from March to September 2020.

Ethics

This study was approved by the Ethical Committe of Faculty of Medicine Universitas Indonesia (Ref. Number: 1454/UN2.F1/ETIK/PPM.00.02/2020).

Study Definition

COVID-19 infection is defined as an RT-PCR confirmed positive COVID-19 from nasopharyngeal swab accompanied by signs and symptoms of COVID-19 and other laboratory examinations that support the diagnosis of COVID-19. Bacterial co-infection is defined as the presence of a pathogen other than SARS-CoV-2 in a COVID-19 patient within the first 48 hours of hospital admission. Secondary bacterial infection was defined as the presence of a pathogen other than SARS-CoV-2 in a COVID-19 patient after the first 48 hours of hospital admission. The microbiological examination was carried out in patients with suspected secondary bacterial co-infection according to the standard of care based on the instruction from the attending physicians.

The degree of COVID-19 is classified according to the World Health Organization (WHO) criteria. Corticosteroids and immunosuppressants, including anti-cytokine agents, calcineurin inhibitors, antimetabolites, and similar therapies were found in the medical records to be used for treating the comorbid prior to COVID-19 infection, as well as for treating the COVID-19 itself once a patient was infected. Procalcitonin (PCT) and c-reactive protein (CRP) values were obtained from laboratory tests performed at the admission. Sepsis and Sequential Organ Failure Assessment (SOFA) score were determined based on the diagnosis in the medical record or the worst SOFA score >2 was obtained during the hospitalization of the patients.

Sample Size and Data Collection

The sample estimate was calculated by considering the prevalence of COVID-19 infection when the study was designed, which was 21%, with a 95% confidence level, and 5% prediction error. Therefore, a sample size of 255 subjects was determined. Data were collected consecutively from the medical records of patients who were hospitalized in Cipto Mangunkusumo Hospital in the period from March 2020 until the required number of samples was achieved.

Outcome Measurement

The outcome measured in this study was the incidence of secondary bacterial infection in COVID-19 and its associated factors.

Statistical Analysis

Demographic and clinical characteristics of patients are presented in percentage, as shown in the table. Variables that are hypothesized to be related to the outcome (secondary bacterial infection) were analyzed univariately. The variables that meet the requirements for multivariate analysis using logistic regression were further analyzed to obtain the odds ratio (OR) value. The value of $p<0.05$ was considered as statistically significant. Data analysis was performed with SPSS version 25.0.

RESULTS

A total of 255 records of hospitalized COVID-19 patients were reviewed. It was found

that 98 subjects (36.5%) were diagnosed with sepsis, 27 subjects (10.6%) had bacterial co-infection, 37 subjects (14.5%) had secondary bacterial infection, and 45 subjects (17.6%) died during hospitalization. **Table 1** shows the demographic data and clinical characteristics.

Of all subjects, the average age was 46 years. The most frequently reported COVID-19 complaints are fatigue, cough, and fever. In the group with secondary bacterial infection, complaints of tachypnea, dyspnea, fatigue, anorexia, myalgia, nausea, vomiting, and decreased consciousness were more common than in the group without secondary bacterial infection. Compared to all subjects with COVID-19, the group with secondary bacterial infection had more comorbidities. The average length of stay for COVID-19 subjects was 11.9 days and the group with secondary bacterial infection has longer length of stay, *i.e.*, 22 days on average.

The group with secondary bacterial infection had a higher proportion of ventilator use, ICU care, corticosteroid and immunosuppressant therapy, sepsis, and in-hospital mortality than the group without secondary bacterial infection. The use of antibiotics in COVID-19 was 100% in the group with secondary bacterial infection and

Table 1. Characteristics of Study Subjects

Characteristics	Total Subject (n=255)	Secondary Bacterial Infection	
		With Secondary Bacterial Infection (n=37)	Without Secondary Bacterial Infection (n=218)
Gender			
Female, n (%)	122 (47.8)	25 (67.6)	101 (50.5)
Male, n (%)	133 (52.2)	12 (32.4)	108 (49.5)
Mean Age, (SD)	46 (16.2)	50 (15.9)	45 (16.2)
Clinical Manifestation			
Fever, n (%)	159 (62.4)	25 (67.6)	134 (61.5)
- Cough, n(%)	183 (71.8)	30 (81.1)	153 (70.2)
- Tachypnea, n (%)	122 (47.8)	30 (81.1)	92 (42.2)
- Dyspnea, n (%)	144 (56.5)	34 (91.9)	110 (50.5)
- Fatigue, n (%)	195 (76.5)	34 (91.9)	161 (73.9)
- Anorexia, n (%)	154 (60.4)	31 (83.8)	123 (56.4)
- Myalgia, n (%)	67 (26.3)	6 (16.2)	61 (28)
- Headache, n (%	34 (13.3)	1 (2.7)	33 (15.8)
- Diarrhea, n (%)	23 (9)	4 (10.8)	19 (8.7)
- Nausea, n (%)	71 (27.8)	17 (45.9)	52 (24.8)
- Vomiting, n (%	28 (11)	8 (21.6)	20 (9.2)
- Anosmia, n (%)	22 (8.6)	1 (2.7)	21 (9,6)
- Ageusia, n (%)	19 (7.5)	1 (2.7)	18 (8,3)
- Loss of consciousness, n (%)	45 (17.6)	21 (56.8)	24 (11)
Comorbidity (based on *Charlson Comorbidity Index*)			
- Without comorbid	106 (41.5)	7 (18.9)	99 (45.5)
- Mild	74 (29)	10 (27.1)	64 (29.4)
- Moderate	48 (18.8)	11 (29.7)	37 (17.0)
- Severe	27 (10.7)	9 (24.3)	18 (8.1)
COVID-19 Severity			
- Mild	138 (54.1)	6 (16.2)	132 (60.5)
- Moderate	22 (8.7)	1 (2.8)	21 (9.6)
- Severe/Critically ill	95 (37.2)	30 (81)	65 (29.9)
Length of stay, mean (SD)	11.9 (9)	22 (13.5)	10 (10)
ICU admission; n(%)	83 (32.5)	27 (73.0)	55 (25.2)
History of hospital admission within the previous 2 weeks; n (%)	101 (39.6)	18 (48.6)	83 (38.1)
History of long-term care, n (%)	59 (23.1)	15 (40.5)	44 (20.2)
CVC placement	43 (16.9)	21 (56.8)	22 (10.1)
History of mechanical ventilation, n (%)	35 (13.7)	18 (48.6)	17 (7.8)
History of corticosteroid consumption, n (%)	90 (35.3)	24 (64.9)	66 (30.3)

History of immunosuppressant consumption, n (%)	86 (33.7)	23 (62.2)	63 (28.9)
Antibiotics treatment, n (%)	210 (82.4)	37 (100)	173 (79.4)
Early antibiotics treatment*, n (%)	170 (81)	31 (83.8)	139 (63.8)
Combination of antibiotics treatment*, n (%)	124 (59)	30 (81.1)	94 (43.1)
Use of Broad-Spectrum Antibiotics*, n (%)	254 (99.5)	37 (100)	217 (99.5)
Organ dysfunction, n (%)	55 (21.6)	21 (56.8)	34 (15.6)
SOFA score, median (IQR)	2 (0-14)	6 (0-13)	0 (0-14)
Bacterial co-infection	27 (11.0)	11 (29.7)	16 (7.3)
Sepsis, n (%)	98 (36.5)	30 (81.1)	63 (28.9)
Mortality during hospitalization, n (%)	45 (17.6)	21 (56.8)	24 (11)

SD: standard deviation, COVID-19: coronavirus disease 2019, ICU: intensive care unit, CVC: central venous catheter
*from subjects receiving antibiotics

79.4% in the group without secondary bacterial infection. 59% of subjects with COVID-19 received combination of antibiotics, including 81% of subjects in the group with a secondary bacterial infection.

Table 2 describes the univariate and multivariate analysis of factors associated with secondary bacterial infection in COVID-19, including age, gender, clinical manifestations, length of stay, ICU care, use of mechanical ventilators, use of central venous catheters, corticosteroid therapy and/or immunosuppression, history of hospitalization in the previous two weeks, history of long-term care, bacterial co-infection, organ dysfunction, sepsis, comorbidities, CRP level, procalcitonin values, and SOFA scores. COVID-19 is classified into mild and moderate to critical groups. CRP level cut-off used in this study was 80 mg/L[7], procalcitonin levels cut-off point was 0.25 ng/ml[8], and SOFA score cut-off point was 2. Prolonged length of stay was determined with the cut-off of 12 days for the group with the length of stay associated with the risk of secondary infection.[9,10]

Table 2. Factors Associated with Secondary Bacterial Infection in COVID-19 Patients.

Variables	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age group (<60 y.o.)	1.1 (0.5 – 2.5)	0.68		
Gender	2.12 (1.0 – 4.4)	0.05	1.5 (0.58 – 4.9)	0.38
Fever	1.30 (0.62 – 2.7)	0.58		
Cough	1.82 (0.76 – 4.35)	0.236	1.0 (0.28 – 3.9)	0.92
Tachypnea	5.8 (2.4 – 13.9)	<0.001	1.4 (0.3 – 6.0)	0.61
Dyspnea	11.1 (3.3 – 37.3)	<0.001	5.31 (1.3 – 21.5)	0.02
Fatigue	4.0 (1.1 – 13.5)	0.02	1.21 (0.1 – 7.46)	0.834
Anorexia	3.99 (1.5 – 9.9)	0.002	1.3 (0.36 – 4.9)	0.657
Myalgia	0.49 (0.19 – 1.25)	0.16	1.82 (0.45 – 7.32)	0.39
Headache	0.1 (0.02 – 1.1)	0.037	0.12 (0.01 – 1.43)	0.095
Diarrhea	1.2 (0.40 – 3.9)	0.755		
Nausea	2.58 (1.2 – 5.2)	0.01	2.2 (0.8 – 5.7)	0.086
Vomiting	2.73 (1.1 – 6.7)	0.04	1.2 (0.24 – 5.7)	0.82
Anosmia	0.26 (0.03 – 1.99)	0.27		
Ageusia	0.309 (0.04 – 2.38)	0.32		
Loss of consciousness	10.6 (4.8 – 23.0)	<0.001	4.81 (1.77 – 13.0)	0.002
COVID-19 severity	7.93 (3.1 – 10.8)	<0.001	0.495 (0.045 – 5.38)	0.564
Length of stay	10.7 (4.5 – 25.8)	<0.001	8.2 (2.9 – 23.3)	<0.001
ICU admission	8.0 (3.6 -17.5)	<0.001	0.95 (0.24 – 3.7)	0.956
History of mechanical ventilation	11.2 (4.9 – 25.0)	<0.001	1.3 (0.28 – 6.1)	0.713
CVC placement	11.6 (5.3 -25.6)	<0.001	3.0 (1.1 – 8.0)	0.023

History of corticosteroid consumption	4.2 (2.0 – 8.8)	<0.001	1.33 (0.08 – 21.8)	0.84
History of immunosuppressant consumption	4.0 (1.9 – 8.3)	<0.001	0.75 (0.2 – 2.2)	0.61
History of hospital admission within the previous 2 weeks	1.54 (0.76 – 3.10)	0.27		
Long-term care	2.6 (1.2 – 5.6)	0.011	1.3 (0.43 – 3.9)	0.622
Organ dysfunction	7.1 (3.3 – 14.9)	<0.001	0.9 (0.1 – 5.5)	0.968
Sepsis	10.5 (4.4 – 25.2)	<0.001	2.3 (0.52 – 10.8)	0.258
Comorbidity	3.48 (1.7 – 7.12)	0.01	1.0 (0.3 – 3.4)	0.917
CRP level	2.7 (1.3 – 5.7)	0.006	1.3 (0.49 – 3.8)	0.537
Procalcitonin level	1.5 (0.74 – 3.0)	0.275		
SOFA score	8.37 (3.8 – 18.1)	<0.001	0.47 (0.11 – 2.0)	0.31
Bacterial co-infection	5.34 (2.2 – 12.7)	<0.001	1.8 (0.52 – 6.44)	0.34

OR: odds ratio, 95% CI: 95% confidence interval, COVID-19: coronavirus disease 2019, ICU: intensive care unit, CVC: central venous catheter, CRP: c-reactive protein, SOFA: sequential organ failure assessment

Based on multivariate analysis, several factors associated with secondary bacterial infection in COVID-19 were complaints of dyspnea (OR 5.31, 95% CI 1.3 – 21.5), decreased consciousness (OR 4.81, 95% CI 1.77 – 13.0), prolonged length of stay (OR 8.2, 95% CI 2.9 – 23.3), and central venous catheter placement (OR 3.0, 95% CI 1.1 – 8.0).

Etiologic Pathogens Cause Secondary Bacterial Infections in COVID-19

Secondary bacterial infection in COVID-19 was determined by the presence of microorganisms other than SARS-CoV-2 that grew from the culture sample after 48 hours of hospitalization. The prevalence of secondary bacterial infection in all study subjects was 14.5%. Of the 255 subjects, 46 subjects (18%) underwent microorganism culture examination.

There was a total of 66 samples used for microorganism culture examination, consisting of 22 blood samples, 32 sputum samples, two bronchoalveolar lavages (BAL) fluid samples, four urine samples, one pleural fluid sample, four wound tissue samples, and one cerebrospinal fluid sample. Of the total 66 samples, 49 samples were positive, and 17 were sterile

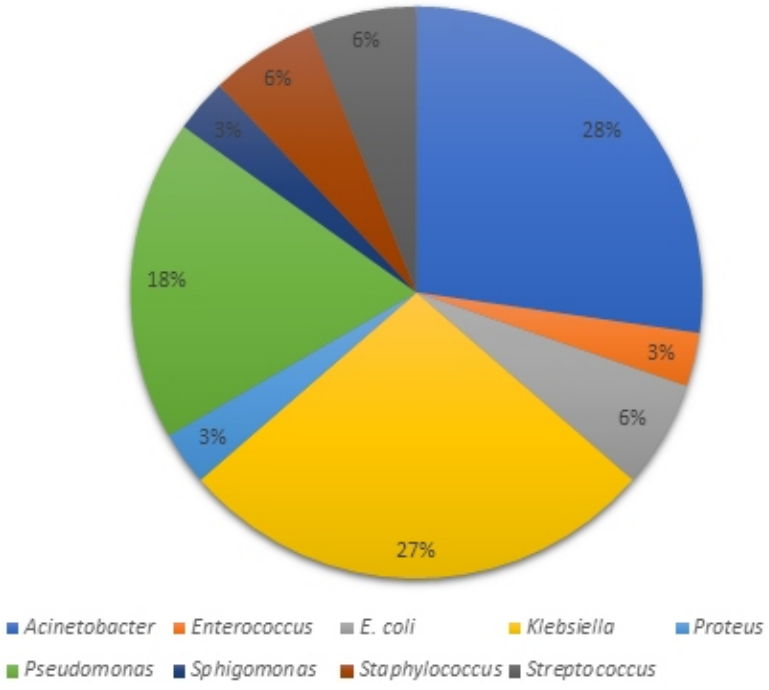

Figure 1. Etiologic Pathogen of Secondary Bacterial Infections in COVID-19

(14 blood culture samples, two urine culture samples, and one BAL fluid culture sample). The secondary bacterial infections found were hospital-acquired pneumonia (27 cases, 73%), catheter-related bloodstream infections (8 cases, 21.6%), and catheter-associated urinary tract infections (2 cases, 5.4%). Pathogenic etiology of secondary bacterial infection is dominated by gram-negative bacteria, *i.e.*, *Acinetobacter* sp. (28%), *Klebsiella* sp. (27%), and *Pseudomonas* sp. (18%). Fungal cultures were found positive in 5 sputum samples that showed the growth of *Candida* sp., and one blood sample showed the growth of *Candida albicans*.

Antibiotics Consumption in COVID-19

Antibiotics were used in 82.4% of subjects, including those without bacterial co-infection and secondary bacterial infection. 99.5% of the antibiotics administered in our subjects were broad-spectrum antibiotics, such as macrolides (33%), cephalosporins (25%), and quinolones (17%). The most frequently used antibiotics in this study was azithromycin from the macrolides, ceftriaxone, cefotaxime, and cefoperazone from the third generation of cephalosporins, and levofloxacin and moxifloxacin from the quinolones (**Figure 2**).

DISCUSSION

In this study, 14.5% of subjects with COVID-19 developed secondary bacterial infection during their hospitalization. Most of the subjects with secondary bacterial infection had severe/critical COVID-19. Approximately 50% of the subjects were admitted to the ICU, on ventilator, treated with corticosteroids and/or immunosuppressants, and diagnosed with sepsis. Mortality was observed in more than half of the subjects in the COVID-19 group with secondary bacterial infection (56.8%). This was much higher than the mortality in the group without secondary bacterial infection (11%).

The prevalence of secondary bacterial infection in COVID-19 in this study is in accordance with data in a systematic review conducted by Langford et al.[4] on 24 COVID-19 studies, where the prevalence of secondary bacterial in patients was 14.3%. A study in Surabaya, Indonesia, showed a prevalence of 19.7%.[11] These two studies also showed an increase in the duration of infection, use of ventilator, and ICU admission in the group with secondary bacterial infections.

COVID-19 infection leads to histological and functional respiratory damage. Histologically,

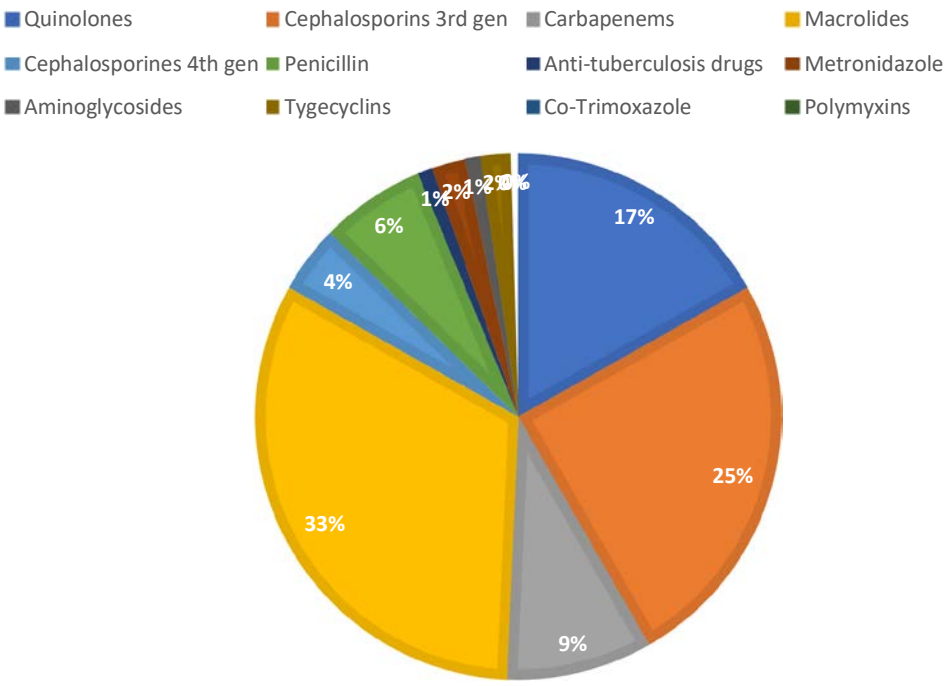

Figure 2. Antibiotic Consumption in COVID-19

cellular damage, goblet cell hyperplasia, increased mucus secretion, mucociliary disturbances, and discoordination may occur. In addition, the alveolar macrophage cells deplete and phagocytes' function is impaired, which cause a decrease in the ability of bacterial clearance by phagocytes and an increase in the rate of bacterial replication. In viral and bacterial co-infection, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are formed. These molecules bind to pattern recognition receptors (PRRs) and activate the formation of interferons (IFNs), cytokines, and chemokines that act as pro-inflammatory molecules, causing more extensive tissue damage.[12–14] The presence of immune dysregulation in both co-infection and secondary bacterial infection in COVID-19 leads to worse clinical manifestations in the COVID-19 group with secondary bacterial infection in this study.

Factors associated with secondary bacterial infection in COVID-19 are dyspnea on admission, decreased consciousness, prolonged hospital stay, and central venous catheter placement during treatment. In this study, dyspnea was experienced by almost all subjects with secondary bacterial infection. The association between the two could be due to complaints of dyspnea which were more common in severe/critical COVID-19 – the predominant grade in the secondary bacterial infection group. However, in multivariate analysis, it was found that the severity of COVID-19 was not associated with secondary bacterial infection, and therefore, the association between dyspnea and secondary bacterial infection appeared to be independent from the degree of COVID-19. Dyspnea was also found in other studies observing secondary bacterial infection in COVID-19, accompanied by fever and gastrointestinal symptoms.[15]

Impaired consciousness is a factor associated with secondary bacterial infection in COVID-19. COVID-19 patients with impaired consciousness have a higher risk of admission to ICU, intubation, need for mechanical ventilation, prolonged length of stay, prolonged need for ventilator, and mortality.[16] In addition, impaired consciousness also acts as an indicator of the severity of COVID-19, even before the respiratory disturbance appears.[17] Therefore, according to this study, impaired consciousness is associated with secondary bacterial infection in COVID-19.

Based on the analysis of this study, the prolonged length of stay for more than 12 days and central venous catheter placement in COVID-19 patients were associated with the risk of secondary bacterial infection. Prolonged treatment is associated with the risk of nosocomial infection, which is mainly related to medical devices and surgical procedures.[10,18–21] The results obtained from this study are in accordance with the results of other studies in COVID-19 patients with secondary bacterial infections. The most common infections reported in this study were pneumonia and catheter-associated bloodstream infections.[22,23] Central venous catheter placement is also associated with an increased risk of nosocomial infection.[24,25] In severe and critically ill COVID-19 patients, the risk of prolonged length of stay was increased, followed by an increase in the duration of use of a central venous catheter, the risk of entry of bacteria through the catheter (catheter as *port d'entrée*), and a decrease in the immune system of the patient, and hence, increased the risk of secondary catheter-related bacterial infection.[24]

All study subjects with secondary bacterial infection received broad-spectrum antibiotics therapy, and so did 80% of subjects without secondary bacterial infection. The same thing was found in another study, with the rate of antibiotics use in COVID-19 patients reached 90%.[4,26] This high number of antibiotics usage can be caused by the difficulties experienced by medical personnel in distinguishing clinical symptoms of bacterial and viral infections, since both have similar manifestations. In addition, at the beginning of the pandemic, administration of macrolide antibiotics, *i.e.*, azithromycin, was still recommended for COVID-19 with or without suspicion of co-infection or secondary bacterial infection, which led to extremely frequent use of it.[27] Cephalosporins and quinolones were also widely used in this study. These two groups were widely used because they are the recommended regimens in the management of community and nosocomial pneumonia in bacterial infections.[28,29]

The frequent use of antibiotics without bacterial infection increases the risk of antibiotic resistance and multi-drug resistant (MDR) bacteria.[30] This is also portrayed by identifying the pathogens causing secondary bacterial infections in this study, which were mostly gram-negative bacteria, *i.e.*, *Acinetobacter* sp., *Klebsiella* sp., and *Pseudomonas* sp. These data are consistent with the annual pattern of nosocomial bacteria and in line with other studies on secondary bacterial infection in COVID-19.[11,22,31,32]

Based on our result, we found that the intensification of proper implementation of antimicrobial stewardship is needed, mainly to prevent the irrational use of antibiotics in COVID-19. Guidelines for secondary bacterial infection in COVID-19, accurate and rapid laboratory investigations, and access to microbiological examinations are the keys in preventing antimicrobial resistance.[32,33]

The limitation of this study is that we used retrospective design with secondary data from medical records. Some of the required data, such as CRP and procalcitonin, were not always available, and only some subjects had the respective tests. In addition, the identification of patients with secondary bacterial infection was determined based on the results of microorganism cultures of patients who were suspected to have secondary bacterial infection. Secondary bacterial infection could not be appropriately identified in subjects without typical clinical characteristics.

CONCLUSION

Secondary bacterial infection was found in 14.5% of hospitalized COVID-19 patients. Factors associated with secondary bacterial infection were complaints of dyspnea on initial admission, decreased consciousness, length of stay of more than 12 days, and central venous catheter placement during treatment. The use of antibiotics in COVID-19 infection was found in 82.4% of subjects and was widely administered to subjects with and without secondary bacterial infection. The use of antibiotics in COVID-19 infection requires special attention to prevent the occurrence of antibiotic resistance.

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