The Use of Antibiotics in COVID-19 Therapy in RSUP Dr. Sardjito Yogyakarta

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ABSTRACT

As a newly emerging disease initially identified at the end of 2019 in Wuhan, China, COVID-19 has various therapeutic options. The current COVID-19 treatment in Indonesia refers to the licensed treatment based on the Emergency Used Authorization from BPOM, which lists many approved antibiotic therapies. However, inappropriate use of antibiotics is known to have an adverse impact of resistance. Therefore, studies on the use of antibiotics in health care facilities, including hospitals, are pivotal, especially in the management of newly emerging disease of COVID-19. This study aims to describe the use of antibiotics as a therapeutic option for COVID-19 treatments in RSUP Dr. Sardjito Yogyakarta. The research used descriptive analytic method by involving patients, who were tested positive for COVID-19 in the period of February to September 2020 in Dr. RSUP Sardjito Yogyakarta, as the research subjects. Data were collected retrospectively using the drug use listed in the medical records. Data were analyzed based on patient characteristics, antibiotic profile, and final prognosis of treatment outcome. This study revealed that the highest cases occurred in men with 69.4%. The productive age group of 21 to 60 years old was known to be the age group with the highest COVID infection (64%). The most widely used antibiotics were azithromycin (56.5%) and levofloxacin (32.9%). The use of antibiotic therapy in COVID-19 patients at RSUP Dr. Sardjito Yogyakarta has proven to be quite effective with a prognostic rate of 76.5% for patients experiencing recovery.
Keywords: Use of Antibiotics; Therapy; COVID-19

INTRODUCTION

The initial COVID-19 outbreak occurred at the end of 2019 in Wuhan, China and has now spread to 215 countries with millions of patients who have been confirmed positive and caused hundreds of thousands casualties worldwide (Tobaiqy et al., 2020). In Indonesia, COVID-19 has been determined as an epidemic since the end of February 2020, and until now tens of thousands of patients were tested positive with thousands of deaths. There has been a rapid surge in the number of positive cases of COVID-19 in Indonesia despite the fact that COVID-19 is a newly emerging disease which has not been provided with much clinical scientific evidence regarding specific therapies for COVID-19 (Kemenkes RI, 2020). The COVID-19 therapy in Indonesia refers to an emergency-basis therapeutic option. This is added by the fact that although there is no comprehensive clinical evidence, drugs with the latest therapeutic priorities can be used on an emergency scale based on the WHO guideline. BPOM has authorized the use of many drugs for COVID-19 therapeutic options in Indonesia, including antibiotics on an emergency basis. Nonetheless, the wide use of antibiotics as a therapeutic

option for COVID-19 is likely to pose a global threat, especially when they are used excessively (BPOM, 2020).

Antibiotics are a class of drugs widely applied to treat infectious diseases attributed to bacteria (Rachmawati et al, 2020). Excessive use of antibiotics may escalate the risk of multiresistant bacteria (BPOM, 2020)The mechanism of antibiotic resistance refers to the ability of antibiotics to reach their site of action or penetrate the outer membrane. Health facilities that are not equipped with any guidelines for the use of antibiotics are likely to pose a threat to incur multiresistance. This is not to mention about the dangerous use of antibiotics without a doctor's prescription, which also serves as an influential factor that may lead to the risk of antibiotic resistance (Rachmawati et al., 2020). Moreover, the actual incidence of bacterial co-infection in this COVID-19 infection still remains unknown. The possible occurrence of this disease is owing to bacterial pneumonia and fungal co-infection, where a greater fungal co-infection occurs due to the use of ventilators in patients (BPOM, 2020). There has been a greater challenge in the efforts to maintain the rational use of antibiotics in this

pandemic era. Therefore, research on the use of antibiotics in COVID-19 therapy in health facilities that handle the care of COVID-19 patients is increasingly essential.

METHOD

This is a descriptive research using a cross sectional approach. The research protocol has received ethical approval number: KE/FK/0998/EC/2020 from the ethics committee of RSUP Dr. Sardjito Yogyakarta. Data were collected from December 2020 to January 2021 at RSUP Dr. Sardjito Yogyakarta. Data were obtained from Excel documents in the form of retrospective recapitulation of medical records. The research population was the data on all COVID-19 patients who were treated at RSUP Dr. Sardjito Yogyakarta from March to October 2020, both for patients with mild, moderate and severe symptoms. The inclusion criteria were determined based on the patient who had received antibiotics and had complete medical records. The collected data were then analyzed descriptively, by including patient characteristics (gender, age, disease complications, and prognosis) and antibiotic profile (type of antibiotic used). Patient characteristics were analyzed descriptively by calculating the percentage of male and female patients, age, disease complications and prognosis. In subsequent, the profile of the use of antibiotics displayed in the form of a percentage was also measured.

RESULTS AND DISCUSSION
Patients' Characteristics

Patients' characteristics in this study included gender, age, disease complications, and prognosis of patients receiving antibiotics (Table 1). The first characteristic of the patient was gender. The collected data indicated the number of male patients exceeded that of the female patients, namely 69.4% and 30.6%, respectively. Men are more susceptible to COVID-19 infection because the X chromosome has protective properties against viruses, and thus generating higher immune system for women against viruses than men's (Parasher, 2021).

Another patient characteristic is age. The research subjects' age was grouped according to age grouping of the Ministry of Health of the Republic of Indonesia (2009): toddlerhood (0-5 years), childhood (5-11 years), early adolescence (12-16 years), late adolescence (17-25 years), early adulthood (26-35 years), late adulthood (36-45 years), early old age (46-55 years), and late old age (56-65 years). These results pinpoint that patients with an age range of 21 – 40 and 41 – 60 years are the largest number of age group to experience COVID-19 infection, each of which with percentage risk of 37.6%. In total, the patients with the most COVID-19 infections at RSUP Dr. Sardjito for the period of March to October 2020 were those aged 21-60 years with a percentage of 75.2% (Table I). Presentation of COVID-19 infection for children at RSUP Dr. Sardjito Yogyakarta was 4.7%. Some research reported that most of the COVID-19 in pediatric patients (81%) experienced mild symptoms or even no symptoms. Pediatric patients who have severe pneumonia, pulmonary edema, ARDS or organ damage were only in a small percentage. However, the Case Fatality Rate (CFR) increased in 50% of patients aged over 80 years old, where the percentage of COVID-19 patients over 80 years old at Dr. Sardjito Yogyakarta was 3.5%. Patients over 80 years old are predisposed to a higher risk of mortality due to their reduced immune function compared to non-geriatric patients.

The research related to complications experienced by patients during the treatment period revealed that many patients suffered from several complications, including; pneumonia, ARDS, COPD, respiratory failure and UTI. The type of complication that most patients suffered was pneumonia (29.4%), which was one of the causes of bacterial co-infection in COVID-19. Complications and comorbidities are risk factors that can cause an increase in the Case Fatality Rate. The increase in the high Case Fatality Rate (CFR) in COVID-19 patients is due to various factors, including; history of chronic diseases, such as diabetes, high blood pressure, heart disease, cerebrovascular disease, digestive disorders, and endocrine system disorders. In many cases, the main culprit of death is respiratory failure, septic shock, or multiple organ failure (Seyed Hosseini et al., 2020).

Antibiotic Usage Profile

Several types of antibiotics were used by patients. The use of antibiotics is the most important therapy in the management of COVID-19 (Wang et al., 2020). When COVID-19

Table I. Characteristics of COVID-19 Patients at RSUP Dr. Sardjito Yogyakarta from March to September 2020

Category	Frequency	Percentage
Gender		
Male	59	69,4%
Female	26	30,6%
Age		
0 – 20 Years Old	4	4,7%
21 – 40 Years Old	32	37,6%
41 – 60 Years Old	32	37,6%
61 – 80 Years Old	14	16,5%
81 – 100 Years Old	3	3,5%
Complications		
Pneumonia	25	29,4%
ARDS	15	17,6%
COPD	10	11,8%
Respiratory Failure	9	10,6%
UTI	5	5,9%

was declared a pandemic, antibiotics were used in all COVID-19 therapies for mild, moderate, or severe symptoms. The use of antibiotics in the treatment of COVID-19 has been proven to be effective in helping prevent or manage secondary bacterial infections and sepsis (Seyed Hosseini et al., 2020).

The use of antibiotics in COVID-19 patients at RSUP Dr. Sardjito Yogyakarta refers to the COVID-19 treatment guidelines set by the Indonesian Lung Doctors Association (PDPI) and is based on the level of infection experienced by the patient. This research was conducted at the initial period of COVID-19 outbreak in Indonesia, namely in March 2020. The guidelines were referred to as the basis for clinical treatments quoted from the initial COVID-19 guidelines, where antibiotics were still recommended as a therapeutic option for COVID-19 management. Some recommended antibiotics that have received the Emergency Used Authorization permit as a COVID-19 therapy by BPOM were azithromycin, levofloxacin, and cefotaxime (BPOM, 2020).

These antibiotics were selected given their broad-spectrum and were prioritized based on the selection of empirical antibiotics (BPOM, 2020). Antibiotics were used in RSUP Dr. Sardjito based on empirical evidence when the patient was diagnosed with infection. Patients experiencing a symptom onset for less than 2 days were provided with antibiotic of strata 1, but if those suffering from infection for more than 2 days would need procalcitonin checking. The patient's with procalcitonin value of more than 0.2 would be provided with strata 2 antibiotics. After the provision of strata 2 antibiotics, the patient would be monitored for 3 days. The patients who did not show improved clinical signs would be de-escalated with strata 3 antibiotics as recommended by the PPRA team (Antimicrobial Resistance Control Program) at the Hospital. The use of empirical antibiotic therapy at RSUP Dr. Sardjito refers to the hospital's bacterial pattern for two years and is grouped according to the Carmelli score, based on risk strata of antibiotic resistance, which is distinguished by Gram staining. Distribution of Carmelli's score stratification at RSUP Dr. Sardjito Yogyakarta for the risk of antibiotic resistance is classified into three strata groups. Strata 1 is provided based on the principle of escalation, by applying antibiotics with low resistance or antibiotics that have a sensitivity of <40% to one or more germs, antibiotics that are used for community infections, and are used for young patients with no comorbidities. Strata 2 are also prescribed based on the principle of escalation, by providing antibiotics that have a moderate risk of antibiotics for infections related to health services. However, it is applied without invasive procedure on patients only to

patients aged > 65 years old, who meet these criteria or patients with comorbidities. In this stratum, the recommended antibiotics are antibiotics that have a sensitivity of 40-69% against one or more germs.

Antibiotics of Strata 3 were provided based on the principle of de-escalation by way of prescribing antibiotics that have a high risk of antibiotic resistance, namely a nosocomial infection, to patients who have been treated for > 5 days and/or have been treated with invasive procedures, patients with immunocompromised status, such as DM patients, cancer patients, HIV-AIDS patients, neutropenia, cystic fibrosis, and patients on immunosuppressant therapy and/or septic patients. Antibiotics in this stratum are antibiotics with a sensitivity of 70% against one or more bacteria and their administration to patients must be based on recommendations from the PPRA team (Antibiotic Resistance Control Program) of the Hospital.

The use of antibiotics to treat infectious diseases caused by viruses can increase drug resistance and increase the risk of allergic reactions. Antibiotics were determined based on the severity of the patient's condition. In addition, it is also based on microbiological patterns and resistance patterns in each hospital. It is not easy to distinguish between infections caused by viruses and bacteria (Vahedi et al, 2020). Infections caused by bacteria, especially in the case of COVID-19 are indicated by an increase in procalcitonin, an increase in White Blood Cell (WBC), an increase in neutrophil numbers, D-Dimer, and C-Reactive Protein (CRP). The increase in procalcitonin that occurs in COVID-19 patients is caused by a bacterial infection (Adebisi et al, 2020). However, not all patients received procalcitonin and D-Dimer examinations. Patients who received the D-Dimer examination were those who were categorized as COVID-19 patients with moderate to severe criteria, while those who received procalcitonin examination were patients who were coinfected with onset of more than two days (Kemenkes, 2021).

Antibiotics for COVID-19

Three antibiotics were used as a therapy for COVID-19 at RSUP Dr. Sardjito Yogyakarta, namely azithromycin with 56.5% of use, levofloxacin with 32.9% and ceftriaxone with 8.2%.

The most widely used antibiotics for COVID-19 therapy at RSUP Dr. Sardjito is Azithromycin with 56.5%. Azithromycin belongs to the macrolide class and is used in a variety of bacterial infections. Apart from their antibacterial activity, macrolides have also shown their activity as an effective antiviral and immunomodulator for the treatment of COVID-19. A retrospective study reported that COVID-19 patients who were given azithromycin with hydroxychloroquine indicated reduced mortality (Damle et al, 2020). At RSUP Dr. Sardjito, 35.3% of patients received combined therapy of azithromycin and hydroxychloroquine.

Azithromycin is commonly combined with meropenem, levofloxacin, ceftazidime, cefixime, amoxicillin, and ceftriaxone. One of the research subjects who suffered from co-infected pneumonio and COPD received azithromycin combined with cefixime, and then escalated with ceftazidime. Azithromycin and clarithromycin in RSUP Dr. Sardjito were given to patients who had nosocomial coinfection from the hospital, based on the assumption that they were infected by ESBL (Extended Spectrum Lactamase) bacteria from the hospital. Nevertheless, no invasive procedure was performed on the patient and such treatment was only prescribed for patients aged > 65 years or patients who have comorbidities at the time of infection. Azithromycin is quite effective antibiotics for preventing lung infections in patients with viral pneumonia. In addition, azithromycin also has a significant anti-inflammatory effect (Damle et al., 2020).

Levofloxacin and ciprofloxacin at RSUP Dr. Sardjito are classified in the strata two class antibiotics, which can be used if the risk of antibiotics is moderate for the infection related to health services. However, the patient is not subjected to invasive procedures, and their infection is generated by ESBL-producing bacteria (Extended Spectrum Lactamase) from the hospital. Such treatment is only administered to patients aged >65 years old with comorbidities. Ceftriaxone was used in cases of COVID-19 for patients with coinfection of community pneumonia without the risk of pseudomonas coinfection. Ceftriaxone or cefotaxime are the therapeutic option for community pneumonia without the risk of pseudomonas coinfection. The recommended dose for ceftriaxone is 1 g every 12 hours iv,

Table II. Overview of Antibiotic Therapy for COVID-19 Patients at RSUP Dr. Sardjito from March to September 2020

Antibiotics	Frequency	Persentage
Azithromycin	48	56,5%
Levofloxacin	28	32,9%
Ceftriaxone	7	8,2%

Table III. Overview of Antibiotic Therapy for Other Infections in COVID-19 Patients at RSUP Dr. Sardjito Yogyakarta from March to September 2020

Antibiotics	Frequency	Persentage
Meropenem	27	31,8%
Ceftazidime	14	16,5%
Amoxicillin	7	8,2%
Cefixime	4	4,7%
Ciprofloxacin	3	3,5%
Cefoperazone Sulbactam	3	3,5%
Clarithromycin	2	2,4%
Moxifloxacin	2	2,4%
Ampicillin	1	1,2%
Cefotaxime	1	1,2%

while cefotaxime is administered 1 g every 8 hours iv.

Antibiotics for Other Infections

In principle, antibiotics are not immediately indicated for COVID-19 patients, but their unavoidable use is attributed to the fact that the patients have to compete to suppress their disease progression. Antibiotic therapy is used in patients with suspected or confirmed cases of superinfection. In cases of suspected superinfection, antibiotics are used as a treatment to prevent nosocomial infections during hospitalization, especially in patients receiving ventilator instrumentation (Liu et al., 2020). In hospitalized patients, those infected with bacterial pneumonia are often clinically similar to those suffering from pneumonia caused by the SARS-CoV-2 Virus. As a result, it is very hard to distinguish whether the patient is infected with the virus by coinfection with hospital-acquired pneumonia or by bacterial co-infection from a ventilator (Adebis, 2020).

The prevalence of bacterial coinfection ranges from 14%-100% in patients in the intensive care unit (ICU) (Heesom et al., 2020). Learning from the 1918 Influenza Pandemic, an estimated of 40 to 50 million deaths worldwide were caused not only by the influenza virus but also by secondary co-infection with Streptococcus pneumoniae (Albin et al., 2020). Viral infection in the respiratory tract itself is said to be a predisposing factor for bacterial and fungal coinfection, which can ultimately lead to death (Tobaiqy et al., 2020). The possibility of coinfection with bacterial and fungal pneumonia will be greater in the group of patients using ventilators to urinary tract infections due to instrumentation (Zhu et al., 2020). Other studies have shown that the high patient mortality rate is not only caused by viral infection, but also due to secondary bacterial coinfection (Adebisi, 2020). In addition, another study revealed that sepsis occurred in 113 patients who died (Alhazzani et al., 2020). Another study conducted in Wuhan China demonstrated that 7.1% of hospitalized patients had fungal coinfection, 32.3% of patients had pneumonia coinfection, 24.6% bacteremia, and 21.5% suffered from urinary tract infection (Chen et al, 2020). At RSUP Dr. Sardjito, 29.4% of patients experiencing bacterial coinfection were coinfected with pneumonia, 11.8% were coinfected with COPD (Chronic Obstructive Pulmonary Disease), and 5.9% were coinfected with UTI (Urine Tract Infection). There are several antibiotics used in the treatment of complications of infection in COVID-19 patients at RSUP Dr. Sardjito including meropenem, ceftazidime, amoxicillin, cefixime, ciprofloxacin,

Table IV. Clinical Outcomes for COVID-19 Patients' Therapy at RSUP Dr. Sardjito Yogyakarta from March to September 2020

Antibiotics	Frequency	Persentage
Recovered	65	76,5%
Dead	20	23,5%

cefoperazone sulbactam, clarithromycin, moxifloxacin, ampicillin, and cefotaxime.

Meropenem is an antibiotic with a sensitivity of 70% against one or more bacteria, and thus it is active against almost all gram-positive and gram-negative bacteria (Rotova et al, 2017). Meropenem is a carbapenem with a beta lactamase inhibitory mechanism by inhibiting peptidoglycan bonds in the cell wall, which can cause autolysis and bacterial cell death (Jason, 2018). At RSUP Dr. Sardjito, meropenem is used for patients who have been hospitalized for more than 5 days, and or have had an invasive procedure but showed no improvement while receiving other antibiotics. The use of meropenem in RSUP Dr. Sardjito amounted to 31.8% for immunocompromised patients with worsening sepsis infection and should be based on recommendations from the PPRA team (Antibiotic Resistance Control Program) of the hospital.

In the case of COVID-19 treatment at RSUP Dr. Sardjito, ceftazidime, ceftriaxone, cefixime and cefotaxime are administered for patients who have not undergone invasive procedures, and those aged more than 65 years old, or patients with comorbidities. Ceftazidime and cefixime are prescribed if the patient's infection is assumed to be an infection from ESBL-producing bacteria (Extended Spectrum Lactamase) from the hospital. 16.5% of COVID-19 patients were given ceftazidime therapy at RSUP Dr. Sardjito for the period of February to September 2020. Ceftazidime is the first therapeutic option in combination with levofloxacin, which is used in ICU inpatients with coinfection with community pneumonia who also have risk factors for infection of pseudomonas (Kemenkes, 2021). In several COVID-19 patients at RSUP Dr. Sardjito from February to September, ceftazidime was often combined with azhthromycin. Such treatment was most likely provided because the patient was also co-infected with pseudomonas. However, the investigators only used secondary data, and did not find patient culture data indicating pseudomonas coinfection. Cefixime is used for patients with a genital infection. Cefixime is provided for COVID-19 patients who suffered from a genital infection as a comorbidity (Bhatraju et al., 2020). The use of cefixime in COVID-19 patients at RSUP Dr. Sardjito Yogyakarta was 4.7%, for those suffering from a urinary tract infection.

Amoxicillin and ampicillin were used in RSUP Dr. Sardjito for young patients without comorbidities, namely in children and in patients with pregnancy. These types of antibiotics were used for patients with coinfection acquired from community pneumonia. 1 patient at RSUP Dr. Sardjito for the period of February to September, a 3-year-old child who was confirmed positive with COVID-19, received empirical ampicillin therapy at a dose of 50 mg/KgBW/6 hours. This is in accordance with the recommended dose for amoxicillin of 500 mg orally every 8 hours, while for ampicillin, it is 50 mg/KgBW every 6 hours intravenously (Kemenkes, 2021). After 5 days of ampicillin provision, the pediatric patient was then escalated to strata 2 antibiotics using ceftriaxone therapy on the 6th day of treatment and on the 11th day of treatment, the pediatric patient was declared cured and was discharged from the hospital.

Therapeutic Clinic Outcomes

After the provision of antibiotic therapy, antiviral and adjuvant therapy based on the symptoms experienced by the patient, the patients showed some clinical outcomes as presented in table IV. It is apparent that the clinical outcome of patients who recovered and were discharged from the hospital was 76,5%, while patients who died were 23,5%.

The limitation of this research lies in the fact that the research was conducted with secondary data that are only made available in the medical record and are not evenly distributed. Researchers plan to present research results with clinical outcome data in the form of parameters for the clinical

laboratory developments of several patients, such as the measurements of leukocytes, erythrocytes, granulocytes, erythrocytes, d-dimer, BUN, creatinine, procalcitonin, CRP, neutrophils, and blood gas analysis. However, the research subjects were patients with COVID-19 who had various symptoms, ranging from mild to severe, the generated data varied based on their level of symptoms, and thus making it hard to analyze and present the data as a whole.

CONCLUSION

The most widely used antibiotic for COVID-19 therapy at RSUP Dr. Sardjito Yogyakarta was azhythromicin with a percentage of use of 56.5%, followed by levofloxacin (32.9%) and ceftriaxone (8.2%). RSUP Dr. Sardjito Yogyakarta is a type A hospital, which is highly referred for the treatment of COVID-19 patients. Therefore, the majority of antibiotic therapy provided to patients is strata 2 and 3 antibiotics, mostly for patients with severe symptoms of COVID-19.

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DECLARATION OF CONFLICTING INTEREST

The authors declare that there is no conflict of interest in this manuscript.

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