Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
Pharmacy and Pharmaceutical Sciences Journal
Published by Faculty of Pharmacy Universitas Airlangga
OPEN ACCESS
E-ISSN 2580-8303
P-ISSN 2406-9388

Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia Vol. 9 No. 2 August 2022, 200-208
DOI: 10.20473/jfiki.v9i22022.200-208
Available online at https://e-journal.unair.ac.id/JFIKI/

Analysis of Antibiotic Use in COVID-19 Patients at a Hospital in Sidoarjo

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Submitted: 9 March 2022
Accepted: 9 August 2022
Published: 31 August 2022

Abstract
***Background**: Antibiotics are given to COVID-19 patients to treat bacterial co-infections, but excessive and inappropriate antibiotic use can increase antibiotic resistance. **Objective:** The study aims to analyze the antibiotic use and bacterial susceptibility in COVID-19 patients at a hospital in Sidoarjo - East Java. **Method:** The research design used was a prospective cross-sectional study using data collection of sputum culture, bacterial susceptibility, medical records, and Pharmacy antibiotics usage from August to October 2021. The Research sample is moderate-to-severe COVID-19 patients. **Result:** The results showed that in August-October 2021, 32 patients met the study sample category, where the most were men (56.25%), age range 46-55 years (31.25%), and outcome recovered as much as 81.25%. The culture results showed that only 1 (one) person out of 32 samples had bacterial growth. The only bacteria that grew in the sputum culture was Enterobacter aerogenes, susceptible to meropenem but resistant to levofloxacin. The highest quantity of antibiotics in this study was levofloxacin 71,16; meropenem 32.25; moxifloxacin 21.84 DDD/ 100 bed days. **Conclusions:** Most of the cases of COVID-19 occurred in men; the age range was 46-55 years, and the outcome recovered was more than those who died. Bacterial co-infection occurred in 3.12% of patients who received meropenem and levofloxacin during their hospitalization. The largest quantity of antibiotics used was levofloxacin, meropenem, and moxifloxacin. The combination of meropenem and levofloxacin should be re-evaluated because levofloxacin is resistant but still susceptible to meropenem.*

***Keywords**: COVID-19, antibiotics resistant, sputum culture, ATC/DDD methodology*

How to cite this article:
Kristanti, W., Yulia, R. & Herawati, H. (2022). Analysis of Antibiotic Use in COVID-19 Patients at a Hospital in Sidoarjo. *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, 9(2), 200-208. http://doi.org/10.20473/jfiki.v9i22022.200-208

INTRODUCTION

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) infection causing current health problems. The World Health Organization (WHO) officially declared the infection as Corona Virus Disease 2019 (COVID-19)in February 2020 (Hu et al., 2021, Wang et al., 2020). COVID-19 is the third pandemic in the 21st century caused by the Corona Virus, with the highest mortality rate (Khan et al., 2021).

The SARS-CoV-2 infection causes various symptoms, such as anosmia, hyposmia, dysgeusia, shortness of breath, dry cough, fever, and weakness. The majority of symptoms occur in the respiratory tract, and radiology examination showed bilateral pneumonia. Other manifestations that occur in COVID-19 include complications in the heart, gastrointestinal, liver, peripheral, and central nerves (Wang et al., 2020; Tsatsakis et al., 2020). The symptoms generally occur in COVID-19 patients, but it should be noted that some people have no symptoms (Setiadi et al., 2020).

SARS-CoV-2 infection was first identified in Wuhan China. The virus has spread not only in China but also to other countries around the world. The cases of COVID-19 continue to increase every day, WHO data until April 11, 2021, shows this pandemic has spread to more than 200 countries around the world with the number of confirmed cases having been infected by this virus as many as 135,057,587 cases and 2,919,932 deaths. The highest cases occurred in America, with 58,025,495 cases and 1,405,254 deaths. In Asia, the number of confirmed cases was 16,177,826 cases and 228,385 deaths.1,437,283 confirmed cases were reported on March 17, 2021, in Indonesia, making Indonesia the country with the highest number of cases in Southeast Asia. Based on a map of the distribution of cases per province in Indonesia, East Java province, as of March 14, 2021, was in the top fourth rank after DKI Jakarta, West Java, and Central Java, with the number of confirmed cases in East Java of 134,595 cases. At the district/ city level, Sidoarjo district ranks second with the highest number of cases in East Java after Surabaya, with 10,481 cases (WHO, 2021; Satgas COVID-19, 2021).

Curative steps for infected patients need to be carried out optimally, although until now, there is no recommendation of drugs and vaccines that have been approved as prophylaxis or treatment of COVID-19 because they are still in the clinical trial stage (Neldi et al., 2020). Therapy is based on pre-existing therapies taking into account the pathogenesis of COVID-19 (Cao et al., 2020). The therapy is expected to reduce the Case Fatality Rate (CFR) in Indonesia. Until now, there is no COVID-19 drug that has received a distribution permit from the National Agency of Drug and Food Control of Indonesia (BPOM). BPOM is still issuing approval for emergency use authorization (EUA) which is expected to increase the cure rate and reduce mortality in COVID-19 patients.

Bacterial co-infection is common in viral infections and a significant reason for morbidity and mortality, but much information is still unknown regarding the incidence of co-infection in COVID-19 patients (Mahmoudi, 2020). One therapy often given to COVID-19 patients is antibiotics to treat co-infection or secondary bacterial infections. In a systematic review of 24 studies involving 3,338 COVID-19 patients who were evaluated for acute bacterial infection, 71.9% of patients received antibiotic treatment, although 3.5% were identified as having co-infection and 14.3% of secondary bacterial infections (Langford et al., 2020). Other studies related to the use of antibiotics in COVID-19 patients were performed on 340 patients, where 43 patients (12.46%) had secondary bacterial infection with Klebsiellasp (25.59%), Methicillin-sensitive staphylococcus aureus (MSSA) (20.93%), Escherichia coli (16.28%), methicillin-resistant staphylococcus aureus (MRSA)(13.95%), Enterobacter sp (11.63%), Streptococcus pneumonia (2.32%) and Pseudomonas aeruginosa (9.30%). The result of the study showed that Enterobacteriaceaeisolates from COVID-19 had the highest resistance to cotrimoxazole (74%), piperacillin (67.5%), ceftazidime (47.5%), and cefepime (42.5%). Data shows that excessive use of antibiotics in the COVID-19 pandemic can pose a risk of multi-resistant bacteria (PDPI et al., 2020). All isolates showed susceptibility to amikacin (100%), and the rate of resistance to oxacillin, erythromycin, and clindamycin was more than 90% (Mahmoudi, 2020). Other risks that can occur when excessive and irrational use of antibiotics are drug toxicity, super-infection risk, prolonged length of stay, and increased cost of treatment (Alldredge et al., 2013; Suda et al., 2014).

Antibiotic resistance is a major problem in human development and a threat to health, affecting the ability to fight several infections (WHO, 2018). One of which is the implementation of an antimicrobial resistance

P-ISSN: 2406-9388
E-ISSN: 2580-8303

control program (PPRA) in hospitals must be aware of antimicrobial resistance control. Evaluation of the implementation of PPRA is carried out through an evaluation of antibiotic use (quantity and quality audit) and monitoring of the emergence and spread of resistant microbes through surveillance of resistant microbes (Kemenkes, 2015).

Standardized methods are required to assess and compare antibiotic use, which is done quantitatively using the anatomical therapeutic chemical (ATC) method for classifying drugs and the defined daily dose (DDD) method for measuring drug use based on WHO recommendations. This method can be used to compare the number of drugs between hospitals and countries (WHO, 2016). A retrospective study in Spain comparing antibiotic use before and during the COVID-19 pandemic using the ATC DDD method resulted in an increase in antibiotic consumption, especially in the intensive care unit (ICU). The rise in the consumption of these antibiotics was in the daptomycin, carbapenem, linezolid, ceftaroline, novel cephalosporin/ beta-lactamase inhibitor, or triazole groups during April – May 2020. Several antibiotics that experienced a significant increase were ceftriaxone, carbapenem, daptomycin, azithromycin, and linezolid (Grau et al., 2021).

Given the lack of information related to antibiotic use in COVID-19 patients, further research is needed to analyze the antibiotic use, the bacterial isolate in sputum samples, and antibiotic susceptibility in moderate-severe COVID-19 patients. This research was conducted at a Hospital in Sidoarjo regency, a national COVID-19 referral hospital that has treated patients with indications of COVID-19 with or without comorbidities.

MATERIAL AND METHODS

The research method used was a prospective cross-sectional study. Data were taken from data collection of sputum culture, bacterial susceptibility, medical records, and antibiotics usage from the Pharmacy from August – October 2021.

The population in this research were COVID-19 patients who were hospitalized in the COVID-19 isolation ward at Sidoarjo Regional General Hospital from August to October 2021. All patients were laboratory-confirmed positive by using RT-PCR. The sample is the population that meets the inclusion and exclusion criteria. The inclusion criteria in this study were all adults (≥18 years old) and moderate-to-severe COVID-19 patients. The exclusion criteria were patients referred to another hospital and pregnant and lactating patients. Sampling was carried out using the consecutive purposive sampling method, where all COVID-19 patients who came and met research criteria according to the research objectives were included in the study until the required number of subjects was met for data analysis. The sample size in this study is the entire sample that meets the criteria, with a minimum sample of 30 (Gay et al., 2012).

Data analysis was carried out descriptively in the form of an overview of bacterial isolates in sputum samples, antibiotic susceptibility, the profile of COVID-19 patients based on therapeutic outcomes during hospitalization, and measuring the antibiotic use using the ATC DDD/ 100 patients bed day method. This research has received ethical approval from the Health Research Ethics Commission of the hospital in the Sidoarjo district with no 893.3/017/438.6.7/2021.

RESULTS

About 32 COVID-19 patients met the inclusion criteria of the study. The sample was taken with a sputum specimen during hospitalization in the isolation ward for culture examination. The demographic features of moderate-severe COVID-19 patients according to Table 1.

Table 1. Demographic Features

Variable	total	Percentage (%)
Gender		
Male	18	56.25
Female	14	43.75
Age		
18-25	2	6.25
26-35	3	9.375
36-45	6	18.75
46-55	10	31.25
56-65	6	18.75
≥ 65	4	12.5

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E-ISSN: 2580-8303

Table 2. Patient Profile Based on Therapeutic Outcome

Therapeutic Outcome	Total	Percentage (%)
Recovered	26	81,25
Died	6	18,75
Total	32	100

Table 3. Culture and Isolated Bacteria

Sputum Culture of Bacteria	Total	Percentage (%)
Negative	31	96.875
Positive	1	3.125
Total	32	100
Bacteria Isolated		
Enterobacteraerogenes	1	100
Total	1	100

Table 4. Antibacterial Susceptibility

		Enterobacteraerogenes
ATC Code	Antibiotic	N (1)
J01CA01	Ampicillin	R
J01CR01	Ampicillin/Sulbactam	R
J01CR05	Piperacillin/Tazobactam	S
J01DB04	Cefazolin	R
J01DD02	Ceftazidime	S
J01DD04	Ceftriaxone	S
J01DE01	Cefepime	S
J01DF01	Aztreonam	S
J01DH03	Ertapenem	S
J01DH02	Meropenem	S
J01GB06	Amikacin	S
J01GB03	Gentamicin	S
J01MA02	Ciprofloxacin	S
J01AA12	Tigecycline	S
J01XE01	Nitrofurantoin	R
J01EE01	Trimethoprim +Sulfamethoxazole	S
J01MA12	Levofloxacin	R

Noted: N = total isolate, R=Resistant, S=Susceptible

Patient profile based on therapeutic outcome

The sample was categorized based on the therapeutic outcome (recovered or died) during hospitalization. According to Table 2. the number of patients recovered was 81.25%and the rest died (18.75%).

Culture and isolation of bacteria

Sputum cultures were obtained from 32 COVID-19 patients. The sputum specimen was then cultured on blood agar and MacConkey agar plates and then incubated for 18-24 hours at 37^0C. One positive culture (3.125%) was obtained, and then the isolated bacteria was identified using the standard microbiological method. The bacteria isolated from sputum culture was *Enterobacteraerogenes*, as shown in Table 3.

Data analysis

Analysis of drug use and drug costs using ABC analysis, where group A with 70%, group B with 20% and group C with 10% of the total drug usage or drug cost.

Antibacterial susceptibility

Isolated bacteria were tested for antibacterial susceptibility based on CSLI M100-S24.[20]The results of antibacterial susceptibility as shown in Table 4.

Suitability of antibiotic use based on antibacterial susceptibility results

The patient with positive sputum culture *Enterobacteraerogenes* had received the combination of levofloxacin 750 mg/24h and meropenem 1 gr/8h antibiotics during hospitalization. Based on the susceptibility results, as shown in table 5, levofloxacin is not suitable, but the use of meropenem is suitable, so

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E-ISSN: 2580-8303

the use combination of meropenem and levofloxacin antibiotics could be overcoming the bacterial infection.

Analysis of antibiotic use based on ATC DDD/100 patient bed days method

During the period August - October 2021, it was found that all samples received antibiotics. The antibiotics were then categorized based on the ATC code recommended by WHO so that 11 groups of antibiotics were obtained. The calculation results of DDD/100-bed days areshown in Table 6.

DISCUSSION

The demographic data showed that the number of males (56.25%) more than females (43.75%), which is according to a study in China that 52% of COVID-19 patients were male as well as a study from Europe which also showed that 72% were male (Jin et al., 2020; Raimondi et al., 2021). The more significant number of males indicates that males experience more severe illness and higher mortality than females (Jin et al., 2020). The difference in the number and severity of males being greater than females in COVID-19 cases could be due to comorbidities and several high-risk behaviours such as smoking by men (Cheng et al., 2021). In addition, the expression of Angiotensin-Converting Enzyme 2 (ACE-2) in males is more significant than in females because of different sex hormones, so males are more easily infected with COVID-19 and have poorer clinical outcomes. However, the relationship between ACE_2 and COVID-19 mortality still needs to be reviewed because other studies have shown that the presence of ACE-2 can protect against organ damage (Biswas et al., 2021).

The highest incidence of COVID-19 in this study occurred at the age of 46-55 years (31.25%), where this age was included in the early elderly category (Kemenkes, 2020). This data is slightly different from other research in that the median incidence of COVID-19 is mainly at 62 years (late elderly) (Jin et al., 2020). COVID-19 could occur at any age, but those aged ≥ 50 years have a significantly higher risk of death (Biswas et al., 2021). Elderly patients face a greater risk of worsening because there will be changes in the body's physiology and the presence of comorbidities. The elderly have natural immunity that decreases with aging, affecting the adaptive and innate immune systems to control viral infection, making them more susceptible to infection (Leng et al., 2010). The elderly are also more vulnerable to unwanted effects from drugs used to treat comorbidities (Lavan et al., 2016). Moderate-severe COVID-19 patients who recovered in this study were 81.25 %, slightly different from another study in that the number of recovered patients in all categories was 96.50 % (Jin et al., 2020).

Table 5. Antibiotics Suitability Based on Antibacterial Susceptibility Results

No	Antibiotic	Antibacterial Susceptibility Result	Suitability
1	Levofloxacin	Resistant	Not suitable
2	Meropenem	Susceptible	Suitable

Table 6. DDD/100 Bed Days COVID-19 patients

No	Antibiotic	ATC code	Route of Administration	DDD WHO Standard	DDD/ 100 Bed Days
1	Levofloxacin	J01MA12	Parenteral	0.5	71.1604
2	Meropenem	J01DH02	Parenteral	3	32.2526
3	Moxifloxacin	J01MA15	Parenteral	0.4	21.8430
4	Ceftazidime	J01DD02	Parenteral	4	8.9590
5	CefoperazoneSulbactam	J01DD62	Parenteral	4	3.0717
6	Azithromycin	J01FA10	Parenteral	0.5	2.9010
7	Ceftriaxone	J01DD04	Parenteral	2	0.1706
8	Amoxicillin and Beta-Lactamase Inhibitor	J01CR02	Parenteral	3	0.1138
9	Metronidazole	J01XD01	Parenteral	1.5	0.1138
10	Azithromycin	J01FA10	Oral	0.3	4.5506
11	Trimethoprim-sulfamethoxazole	J01EE01	Oral	NA	-

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Radiology finds that COVID-19 patients are often characterized by the presence of pneumonia that is difficult to distinguish between bacterial or viral causes, so clinicians provide antibiotic therapy. In this study, all subjects received antibiotic therapy. In COVID-19 patients, antibiotic therapy is generally not recommended unless bacterial pneumonia is proven. Giving antibiotics to COVID-19 patients must be careful because they have the potential for excessive use in the COVID-19 pandemic era, which can become a global threat to the increase in the incidence of multi-resistant bacteria (Alldredge et al., 2013).In patients with the possibility of bacterial pneumonia, antibiotic therapy with first-line empirical antibiotics can be given, daily re-evaluation is carried out, and if there is no evidence of bacterial infection, then de-escalation or discontinuation of antibiotics is carried out.55 Therapeutic guidelines for CAP (Community-Acquired Pneumonia), which is not severe, the recommended therapy regimen is a combination of beta-lactam + macrolide or a single respiratory fluoroquinolone. In contrast, for patients in the severe category, beta-lactam + macrolide/ beta-lactam + respiratory fluoroquinolone can be used (Joshua et al., 2019). Fluoroquinolones, carbapenems, protein synthetase inhibitors, cephalosporins, beta-lactams, metronidazole, and cotrimoxazole were the antibiotics used by the patients in this study. The group that was mostly used was fluoroquinolones, followed by carbapenems. The fluoroquinolones used in COVID-19 patients in this study were moxifloxacin or levofloxacin, while the carbapenem group used meropenem. Fluoroquinolones are a group of antibiotics that have a broad spectrum. Fluoroquinolones have the potential as antivirals to suppress the replication of multiple positive-sense viruses and single-stranded RNA viruses such as dengue virus, zika virus, rhinovirus, and hepatitis C virus, presumably through the mechanism of interference with viral entry and viral helicase inhibition. A study was conducted to determine the antiviral potential of fluoroquinolones (enoxine, ciprofloxacin, levofloxacin, and moxifloxacin) and yielded data that these fluoroquinolones are not suitable antivirals for COVID-19 (Scroggs et al., 2020). Patients in this study also received meropenem which is generally combined with fluoroquinolone. The administration of fluoroquinolones and meropenem is by the therapeutic guidelines, but the administration is only for bacterial pneumonia. Evaluation of the antibiotics utilization quantitatively was then carried out using the method recommended by WHO, namely ATC DDD/100 bed days. The DDD/100 bed days of antibiotic treatment calculation in moderate-to-severe COVID-19 patients from August to October 2021 obtained a total result of 145.1365 DDD/100 bed days. Levofloxacin is an antibiotic with the highest value, 71.16 DDD/bed days, followed by meropenem 32.25 and moxifloxacin at 21.84 DDD/100 bed days. This study is similar to a study that analyzed the antibiotics utilization with the ATC DDD/ 100 bed days method in the early COVID-19 pandemic where there was the use of beta-lactam antibiotics (ceftriaxone, carbapenems, cephalosporins/beta-lactamase inhibitors) and azithromycin in a hospital (Gay et al., 2012). Another study stated that the most antibiotics given to COVID-19 patients were azithromycin, levofloxacin, and ceftriaxone, with the value of DDD/bed days respectively 48.12; 44.01; and 21.13 DDD/ 100 bed days (Putra et al., 2021). Sputum cultures of COVID-19 patients were carried out on research samples and observed bacteria growing to determine the possibility of bacterial co-infection in patients. From the total sample of the study, 32 specimens of sputum were obtained, but only one specimen (3.125%) experienced bacterial growth. The bacteria that grew in the sputum specimen was Enterobacteraerogenes. Enterobacteraerogenes is commonly found in the human gastrointestinal tract and does not cause health problems in healthy humans (Bains et al., 2020). This bacteria was found in COVID-19 patients in another research (Catano-correa et al., 2021). Based on the percentage of samples containing bacteria in the sputum of COVID-19 patients, the bacterial co-infection in this study was 3.125%, where the results were not different from existing meta-analysis studies, namely the incidence of co-infection in COVID-19 patients was 3.5% (PDPI et al 2020). Other bacteria were not found in the other 31 sputum because the infection was caused by the covid-19 virus without bacterial co-infection. The covid-19 virus is the cause of pneumonia experienced by patients. Administration of antibiotics for COVID-19 patients requires further review because COVID-19 infection is caused by a virus, not bacteria, unless the patient has a bacterial co-infection. This low proportion of bacterial co-infections in COVID-19 patients indicates that antibiotics are not appropriate for COVID-19 patients unless it is proven that the patient has bacterial co-infection.

P-ISSN: 2406-9388
E-ISSN: 2580-8303

In this study, isolate that were positive experienced bacterial growth and then tested for antibiotic susceptibility. The results of these tests revealed various types of data susceptibility and resistance. Piperazine/tazobactam, ceftazidime, ceftriaxone, cefepime, aztreonam, ertapenem, meropenem, amikacin, gentamicin, ciprofloxacin, tigecycline, and trimethoprim + sulfamethoxazole were all effective against the isolate. At the same time, the isolates showed resistance to the antibiotics ampicillin, ampicillin-sulbactam, cefazolin, nitrofurantoin, and levofloxacin. The research samples were taken from the sputum, and the isolates experienced the growth of Enterobacteraerogenes bacteria in this study, receiving antibiotic levofloxacin 750 mg and meropenem 1 gr. Based on the antibiotic sensitivity test data, the use of meropenem was appropriate because the isolates still showed susceptibility to the antibiotic, but not for the benefit of levofloxacin because the isolates showed resistance to the antibiotic. Although the results of the susceptibility test of levofloxacin are resistant bacteria, the bacterial co-infection in this patient can still be overcome by meropenem, where meropenem is a broad-spectrum antibiotic group and is still susceptible based on the results of the bacterial sensitivity test.

Based on the culture and bacterial susceptibility test results, which were only obtained from 1 (one) research sample, other studies related to bacterial co-infection in COVID-19 patients are needed as comparison material.

CONCLUSION

Most of the cases of COVID-19 occurred in men; the age range was 46-55 years, and the outcome recovered was more than those who died. Bacterial co-infection occurred in 3.12% of patients, where they received meropenem and levofloxacin during their hospitalization. The most significant quantity of antibiotics used was levofloxacin, meropenem, and moxifloxacin. The combination of meropenem and levofloxacin should be re-evaluated because levofloxacin is resistant but still susceptible to meropenem.

ACKNOWLEDGEMENT

We thank all hospital staff, patients, and supervisors involved in this research.

AUTHOR CONTRIBUTIONS

Conceptualization, R.Y., F.H.; Methodology, R.Y., F.H.; Validation, W.K. F.H.; Formal Analysis, W.K. F.H.; Investigation, W.K.; Resources, W.K.; Data Curation, W.K.; Writing - Original Draft, W.K. F.H.; Writing - Review & Editing, W.K. F.H., R.Y.; Supervision, W.K..; Project Administration, F.H., R.Y.; Funding Acquisition, R.Y.

CONFLICT OF INTEREST

The authors report no conflict of interest in this study.

REFERENCES

Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, et al. (2013). Applied Therapeutics: The Clinical Use of Drugs. *Wolter Kluwer Health*. *10*: 1437-1460.

Bains K, Seo DJ, Wang J, et al. (2020). Recurrent High-Grade Enterobacter aerogenes Bacteremia in a Patient with Hepatocellular Carcinoma. *AJG*; *S1739*. doi: 10.14309/01.ajg.0000715408.97311.c5

Biswas M., Rahaman S., Biswas T.K., et al. (2021). Association of Sex, Age and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. *Intervirology*. *64*; 36 - 47. doi: 10.1159/ 000512592

Cao B, Wen D, Liu W, Wang J, Fan G, Ruan L, et al. (2020). A trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe COVID-19. *N Engl J Med*. *382 (19);* 1787 - 1798. doi: 10.1056/NEJMoa2001282

Cheng S, Zhao Y, Wang F et al. (2021). Comorbidities Potential Impact on Severe and Non-severe Patients with COVID-19. *Medicine.100;*12. doi: 10.1097/MD.0000000000024971

Clinical Laboratory Standards Institute (CLSI). (2014). M100-24 Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement. *34(1);* 1-106

Catano-Correa JC, Cardona-Arias JA, Mancilla JPP, et al. (2021). Bacterial Superinfection in Adults with COVID-19 Hospitalized in Two Clinics in Medellin-Colombia.*Plos One*. 1-12. doi: 10.1371/journal.pone.0254671

COVID-19 STP. PetaSebaranCOVID-19. (2021). https://covid19.go.id/peta-sebaran. Accessed: 14 Maret 2021.

Gay L.R, Mills G.E., Airasian P. (2012). Educational Research: Competencies for analysis and applications. 10th ed. *Pearson Inc. Boston*.

Grau S, Echeverria-Esnal D, Gomez-Zorilla S, Navarrete-Rouco ME, Masclans JR, Espona M, et al. (2021). Evolution of Antimicrobial Consumption During the First Wave of COVID-19 Pandemic. *Antibiotics.10 (132);* 1-11. doi: 10.3390/antibiotics10020132

Hu B, Guo H, Zhou P, Shi Z. (2021). Characteristics of SARS-CoV-2 and COVID-19. Microbiology.19; 141 - 152. doi: 10.1038/s41579-020-00459-7

Jin J-M, Bai P, He W et al. (2020). Gender Differences in Patients with COVID-19: Focus on Severity and Mortality. Front. PublicHealth. 8; 152. doi: 10.3389/fpubh.2020.00152

Joshua P. Metlay*, Grant W. Waterer*, et al. (2019). Diagnosis and Treatment of Adults with Community-acquired Pneumonia An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. American Thoracic Society and Infectious Diseases Society of America. *Am J RespirCrit Care Med. 200*, e45–e67. doi: 10.1164/rccm.201908-1581ST

Kementerian Kesehatan Republik Indonesia. (2020). Profil Kesehatan Indonesia 2019. Jakarta.

Kementerian Kesehatan Republik Indonesia. (2015). Program Pengendalian Resistensi Antimikroba di Rumah Sakit. Jakarta.

Khan M, Adil SF, Alkhathlan HZ, Tahir MN, Saif S, Khan M, et al. (2021). COVID-19: A Global Challenge with Old History, Epidemiology, and Progress so Far. *Molecules.26 (39);* 1-20. doi: 10.3390/molecules26010039

Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. (2020). Bacterial Co-infection and Secondary Infection with COVID-19: A Living Rapid Review and Meta-analysis. *Clinical Microbiology and Infection*. 26; 1622-1629. doi: 10.1016/j.cmi.2020.07.016

Lavan AH, Gallagher P. (2016). Predicting Risk of Adverse Drug Reactions in Older Adults. *TherAdv* Drug Saf. 7 (1); 11-22. doi: 10.1177/2042098615615472

Leng J, Goldstein DR. (2010). Impact of Aging on Viral Infections. Microbes Infect.12 (14-15); 1120-4. doi: 10.1016/j.micinf.2010.08.009

Mahmoudi H. (2020). Bacterial Co-infection and Antibiotic Resistance in Patients with COVID-19. GMS Hygiene and Infection Control. 15; 1-26. doi: 10.3205/dgkh000370.

Neldi V, Suharjono. (2020). Remdesivir: Mechanism and Effectiveness for Coronavirus Disease 2019 (COVID-19). *Pharmaceutical Sciences and Research.7;* 39-48.

PDPI, PERKI, PAPDI, PERDATIN, IDAI. (2020). Pedoman Tatalaksana COVID-19. *3*;1-46

Putra DE, Retnoningrum D, Arkhaesi N, et al. (2021). Pola Pemberian Antibiotik di Era Pandemi COVID-19 (Studi Kasus di Rumah Sakit Nasional Diponegoro). *Med Hosp.8(2)*; 194-199. doi: 10.36408/mhjcm.v8i2.578

Raimondi F, Novelli L, Ghirardi A, et al. (2021). COVID-19, and Gender: Lower Rate but Same Mortality of Severe Disease in Women-an Observational Study. *BMC Pulm Med. 21;* 96. doi: 10.1186/s12890-021-01455-0.

Scroggs S.L.P, OfferdahlD.K, Flather D.P, Morris C.N, Kendall B.L, Broeckel R.M, et al. (2020). Fluoroquinolone Antibiotics Exhibit Low Antiviral Activity against SARS-CoV-2 and MERS-CoV. *Viruses*. *13(8)*:2-12. doi: 10.3390/v13010008.

Setiadi AP, Wibowo YI, Halim SV, Brata C, Presley B, Setiawan E. (2020). Tata Laksana Terapi Pasien dengan COVID-19 : Sebuah Kajian Naratif. Jurnal Farmasi Klinik Indonesia. *9(1);* 70-94.

Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Taylor TH. (2014). Trends and Seasonal Variation in Outpatient Antibiotic Prescription Rates in the United States, 2006-2010. *AAC Journal*. *58(5);* 2763-2765. doi: 10.1128/AAC.02239-13

Tsatsakis A, Calina D, Falzone L, Petrakis D, Mitrut R, Slokas V, et al. (2020). SARS-CoV-2 Pathophysiology and its Clinical Implication: An Integrative Overview of the Pharmacotherapeutic Management of COVID-19. *Food and Chemical Toxicology*. *146 (111769*); 1 - 14. doi: 10.1016/ j.fct.2020.111769

Wang M, Zhao R, Gao L, Gao X, Wang D, Cao J. (2020). SARS-CoV-2: Structure, Biology, and Structure-based Therapeutics Development. *Frontiers in cellular and infection microbiology*. *10;* 1-14. doi: 10.3389/fcimb.2020.587269

World Health Organization. (2021). WHO Coronavirus (COVID-19). https://covid19.who.int/table. Accessed: 11 April 2021

World Health Organization. (2018). WHO Report on Surveillance of Antibiotic Consumption.Switzerland.

World Health Organization. (2016). WHO Methodology for a Global Program on Surveillance of Antimicrobial Consumption. *1;* 1-12.