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Original Article

Quantity of antibiotic use and its association with clinical outcomes in COVID-19 patients: A snapshot from a provincial referral hospital in Indonesia

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Abstract

Irrational antibiotic use in Indonesia is considered high, yet there are still lacks reliable information regarding the issue. The quantity of antibiotic use studies, in particular during coronavirus disease 2019 (COVID-19) pandemic, was not well reported. The aim of this study was to evaluate antibiotic use in COVID-19 patients at a province referral hospital in Aceh, Indonesia, Dr Zainoel Abidin Hospital, and to assess the association between antibiotic use and COVID-19 clinical outcomes. The defined daily dose (DDD) method was used and expressed in DDDs per 100 patient-days as in hospital setting. The data were obtained from inpatient confirmed COVID-19 patients between March 2020 and December 2021. A logistic regression was used to determine the association between patients' characteristics and antibiotic usage with clinical outcomes. A total of 361 treated COVID-19 patients were included using a random sampling technique and analyzed. Out of 361 patients, 89.2% of them were treated with antibiotic(s). All the antibiotics were given empirically except for cefazoline (5.5%) that was used as prophylaxis to obstetric patients who underwent the c-section. Azithromycin was the most prescribed antibiotic and levofloxacin had the highest DDD. Our data suggested that there was no association between antibiotic use and clinical outcomes of COVID-19 patients (p=0.128). Having sepsis and another pulmonary disease however were associated with mortality of COVID-19 patients with adjusted odds ratio (aOR) 14.14; 95%CI 2.94–67.90, p=0.001 and aOR 8.64; 95%CI 3.30–22.63, p<0.001, respectively. In addition, patients older than 60-year-old had a higher chance to an unfavorable outcome compared to those younger than 30-year-old, aOR: 7.61; 95%CI: 1.07–53.94. In conclusion, the use of antibiotics is prevalent among COVID-19 and it is not directly associated with clinical outcomes.

Keywords: COVID-19, antibiotic, clinical outcome, defined daily dose, pharmacoepidemiology

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Introduction

The coronavirus disease 2019 (COVID-19) spread rapidly without control during the early days of the pandemic. Antibiotic was considered one of the drugs of choice to treat the disease,

Received: July 24, 2023 - Accepted: December 25, 2023 - Published online: December 25, 2023

however, the specific treatment was not discovered yet [1]. Antimicrobial resistance has been a serious global concern [2]. The majority of patients with COVID-19 were given antibiotics despite the insufficient bacterial infection evidence [3]. Doctors were alarmed by the complexity of the disease and to avoid the uncertain complications, prophylaxis or empiric antibiotic was given to the patients [4].

At least 70% of COVID-19 patients were prescribed antibiotics empirically, and broad-spectrum was commonly used in most cases [5]. Antifungals were also reported to be used in 15% of patients [3]. A meta-analysis study reported that 82% of COVID-19 patients in 42 countries received antibiotic treatment without clear indication [6]. Indonesia is still lacking data regarding the issue. An estimated 75–90% population of Indonesia were reported to received antibiotic empirically. One center in Surabaya, Indonesia, reported that 75.2% of the patients received antibiotics before culture confirmation, while only 19.7% were confirmed positive for bacterial infections [7].

The increased number of antibiotic usage during the pandemic to treat COVID-19 should be a major concern, these antibiotics (i.e., azithromycin, vancomycin, carbapenem, tigecycline, ceftriaxone, and linezolid) were considered as critically important antimicrobials (CIA) for human medicine [8,9]. Defined daily dose (DDD) is a common method to measure antibiotic usage by estimating the average maintenance dose of drug utilization (in adult patients). In this manner, the measurement would not have to include discrepancies in pharmaceutical preparations, international standards, or even changes in drug costs. DDD is relatively easy and inexpensive to document and evaluate therapy intensity in many drug classes [10,11].

The aim of this study was to evaluate the quantity of antibiotic use in treated COVID-19 patients by using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC)/DDD method at a provincial referral hospital in Indonesia as well as to determine its association to COVID-19 patients' outcome. The results may potentially contribute to future studies including basic data or comparisons of antibiotic usage.

Methods

Study design and setting

The study was conducted using retrospective data from medical records of treated COVID-19 patients at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. The hospital was appointed as one of the referral center hospitals for COVID-19 in Aceh by the Indonesian Ministry of Health as part of the COVID-19 Response Acceleration Task Force. The obtained data on epidemiological characteristics, clinical status, microbiology data, and antibiotic use of the patients from March 2020 until December 2021 were analyzed to identify the association between the mentioned data and COVID-19 patient outcomes.

Sample size and randomization

There were 3,361 treated confirmed COVID-19 at Dr. Zainoel Abidin Hospital recorded from March 2020 until December 2021. The minimum sample size was 310 patients, calculated using the necessary sample size with an accuracy of 95% and a margin of error of 0.05 [12]. The prevalence of empirical antibiotics used in COVID-19 patients was 71.9%, according to a previous study [13].

Patients

All PCR-confirmed COVID-19 patients were considered eligible for the study. Patients with comorbidities, such as hypertension and cardiovascular disease, diabetes mellitus type 2, chronic kidney disease, cancer survivor and malignancy, and those with over 14 days of hospitalization were excluded from the study.

Study variables and data collection

The obtained data included in this study were details of COVID-19 severity, age, gender, length of stay (LOS), clinical outcome, complication that could worsen the prognosis (recorded as secondary diagnosis), microbiological examination, antibiotic type in use, dosage, and duration

of therapy. COVID-19 severity and secondary diagnosis were assessed by the doctor in charge of the patient, and some patients might have more than one secondary diagnosis. The dependent variables were COVID-19 severity and clinical outcome whilst patient characteristics and antibiotic usage were independent variables.

All the inpatients were screened before hospitalization. The 4th National Guidelines for COVID-19 of Indonesia categorized COVID-19 severity into four main categories based on the patient's clinical condition: mild, moderate, severe, and critically ill. Mild illness was defined by various signs and symptoms of COVID-19 without signs of typical pneumonia (shortness of breath, dyspnea, or abnormal chest imaging). Moderate illness was considered when signs of typical pneumonia were present during the examination, or there was any evidence of lower respiratory disease but oxygen saturation (SpO_2) measured remained over 93%. Severe illness patients appeared to have severe respiratory distress or SpO_2 measurement below 93%. Critical illness patients had progressed symptoms that lead to acute respiratory distress syndrome (ARDS), sepsis, shock, or require a mechanical ventilator or vasopressors to survive. COVID-19 severity was divided into two categories in this study; mild to moderate illnesses were grouped into non-severe and severe to critical illness were grouped into severe.

Patients' outcome was categorized into two categories into recovered and deceased. The recovered patients were COVID-19 inpatients that improved clinical conditions and was allowed to be de-isolated from the hospital. Deceased patients were considered COVID-19 inpatients who died at Dr. Zainoel Abidin Hospital after at least one day of treatment.

Age was classified into 4 groups: ≤30 years, 31–45 years, 46–59 years, and ≥60 years. Patients' LOS that was included in this study were patients that was hospitalized for 1 to 14 days. Accumulation of all inpatients' LOS was counted as it was needed in DDD calculation as a denominator. DDD calculation in this study was expressed in DDDs per 100 patient days to evaluate antibiotic consumption in the hospital setting.

Statistical analysis

A logistic regression was used to determine association between patients' characteristics and antibiotic use with clinical outcomes with a confidence interval of 95% and a significance level of 5%. All variable with $p<0.25$ in univariate logistic regression analyses were included in multivariate analysis. All statistical analyses were conducted using SPSS program version 25.0 (SPSS, IBM, New York, US).

Results

A total of 361 patients were included in this study, there were 258 non-severe COVID-19 patients (71.5%), and 103 severe COVID-19 patients (28.5%). Univariate analysis is described in **Table 1**. The association between antibacterial usage and the patient's clinical outcome is shown in **Table 2,** while the association between the patient's characteristics and the patient's clinical outcome is seen in **Table 3**.

Antibiotic profiles

There were 17 types of antibiotics prescribed to COVID-19 inpatients during the first two years of the pandemic at Dr. Zainoel Abidin Hospital of which azithromycin was the mostly prescribed (43.5%). According to the dosage and duration of therapy, levofloxacin had the highest DDD (by total accumulation of oral and parenteral administration) with 97.94 DDD/100 patient days, followed by azithromycin (56.33 DDD/100 patient days), and ceftriaxone (15.15 DDD/100 patient days).

During the early stages of the pandemic, culture examination was tested only on a few cases, especially in severe conditions. There were 52 isolates from 38 out of 361 patients included in this study. This was one of the reasons why all antibiotics in this study were used empirically, except for cefazoline was used as prophylaxis to obstetric patients that underwent c-sections. Based on WHO's AWaRe (Access, Watch, Reserve) classification, most antibiotics were in the 'Watch' category.

A total of 37 patients (10.25%) had no antibiotic prescription for treatment at the hospital. All of them had mild to moderate symptoms, except for one patient that was critically ill on arrival

and died after one day of hospitalization. In this study, one anti-parasitic (hydroxychloroquine) and one anti-fungal (micafungin) were identified for prescription.

Table 1. Univariate analysis of antibiotic usage using defined daily dose (DDD) method (n=361)

DDD code	Antibiotic	ATC/ WHO	Total use (gram)	Total DDD	DDD/patient Total DDD/LOS*) x 100	Total	%
J01FA10	Azithromycin (O)	0.3	387.50	1291.67	56.33	157	43.5
J01MA12	Levofloxacin (P/O)	0.5	571.5	2145.83	97.94	120	33.2
J01DD04	Ceftriaxone (P)	2.0	695	347.50	15.15	75	20.8
J01DD08	Cefixime (O)	0.4	111.20	278	12.12	68	18.8
J01DB04	Cefazoline (P)	3.0	62	20.67	0.90	20	5.5
J01DH02	Meropenem (P)	3.0	293	97.67	4.26	18	4.9
J01MA02	Ciprofloxacin (O)	1.0	47	156.67	6.83	10	2.8
J01XD01	Metronidazole (P)	1.5	69	46	2.01	8	2.2
J01XA01	Vancomycin (P)	2.0	31	3.44	0.15	5	1.4
J01DD02	Ceftazidime (P)	3.0	76	19	0.83	5	1.4
J01FF01	Clindamycin (O)	1.2	19.20	16	0.70	4	1.1
J01DB05	Cefadroxil (O)	2.0	17.50	8.75	0.38	4	1.1
P01AB01	Metronidazole (O)	2.0	19.50	9.75	0.43	3	0.8
J01CA01	Ampicillin (P)	6.0	63	10.50	0.46	3	0.8
J01DD12	Cefoperazone (P)	4.0	40	10	0.44	3	0.8
J01XX08	Linezolid (P)	1.2	4.80	4	0.17	2	0.6
J01MA14	Moxifloxacin (O)	0.4	2.40	6	0.26	2	0.6
J01XX01	Fosfomycin (P)	8.0	6	0.75	0.03	1	0.3
J01MA02	Ciprofloxacin (P)	0.8	0.40	1.33	0.06	1	0.3
P01BA02	Hydroxychloroquine (O)	0.516	0.40	0.20	0.01	1	0.3
J02XA05	Micafungin (P)	0.1	0.40	0.20	0.01	1	0.3
J01CR05	Piperacillin/ Tazobactam (P)	14	32	10.67	0.47	1	0.3
Total						537	100

O: oral; P: parenteral
*LOS accumulation of 361 patients with a total 2,293 days (patients without antibiotic prescriptions were also included)

Association between antibiotic usage and clinical outcomes

There were no significant association between antibiotic usage and clinical outcome of COVID-19 patients in this study (p=0.128).

Table 2. Association between antibiotic usage and COVID-19 inpatients' clinical outcome

Antibiotics	Recovered (n = 322)	Deceased (n = 39)	Total (n = 361)	Unadjusted OR (95% CI)	p-value
Prescribed	286 (88.8%)	38 (97.4%)	324 (89.8%)	4.78 (0.64–35.90)	0.128
Not prescribed	36 (11.2%)	1 (2.6%)	37 (10.2%)	Ref	

Association between patients' characteristics and COVID-19 clinical outcome

Our data indicated that patient age and having sepsis or another pulmonary disease were associated with mortality. Patients' ages ranged between 13 to 90 years, with a median age of 44 (±15.54) years. Independently, the older the patient, the greater the risk of developing to severely ill conditions and worser clinical outcomes. Among the four categories, ≥60 years old patients had the largest proportion of COVID-19 mortality.

Having sepsis and another pulmonary disease had a significant association with COVID-19 mortality. COVID-19 patients with sepsis were likely to have a 14-fold risk (p=0.001) of mortality than those without the complication. ARDS found in this study was diagnosed in critically ill patients. Along with other pulmonary diseases, ARDS was categorized under "other pulmonary disease". This category contributed negatively and patients with the condition might have 8-fold (p<0.001) risk of mortality.

Table 3. Association between patients' characteristics and COVID-19 inpatients' clinical outcome

Variables	Recovered (n=322)	Deceased (n=39)	Total (n=361)	Unadjusted		Adjusted	
				OR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Age (years)							
≤30	70 (21.7%)	2 (5.1%)	72 (19.9%)	Ref		Ref	
31–45	111 (34.5%)	8 (20.5%)	119 (33%)	2.52 (0.52–12.22)	0.250	1.22 (0.16–9.34)	0.856
46–59	84 (26.1%)	12 (30.8%)	96 (26.6%)	5.00 (1.08–23.09)	0.039*	3.11 (0.43–22.52)	0.262
≥ 60	57 (17.2%)	17 (43.6%)	74 (20.5%)	10.44 (2.32–47.08)	0.002*	7.61 (1.07–53.94)	0.042*
Gender							
Male	158 (49.1%)	24 (61.5%)	182 (50.4%)	1.66 (0.84–3.28)	0.144	0.975 (0.41–2.31)	0.954
Female	164 (50.9%)	15 (38.5%)	179 (49.6%)	Ref		Ref	
Secondary diagnosis							
Sepsis							
Yes	5 (1.6%)	15 (38.5%)	20 (5.5%)	39.63 (13.3–118.31)	<0.001**	14.14 (2.94–67.90)	0.001*
No	317 (98.4%)	24 (61.5%)	341 (94.5%)	Ref		Ref	
Pneumonia							
Yes	14 (4.3%)	12 (30.8%)	26 (7.2%)	9.78 (4.11–23.24)	<0.001**	1.63 (0.39–6.92)	0.505
No	308 (95.7%)	27 (69.8%)	335 (92.8%)	Ref		Ref	
Other pulmonary disease							
Yes	17 (5.3%)	22 (56.4%)	39 (10.8%)	23.22 (10.44–51.65)	<0.001**	8.64 (3.30–22.63)	<0.001**
No	305 (94.7%)	17 (43.6%)	322 (89.2%)	Ref		Ref	
Microthrombosis							
Yes	156 (48.4%)	28 (71.8%)	184 (51%)	2.71 (1.30–5.63)	0.008*	1.39 (0.54–3.56)	0.492
No	166 (51.6%)	11 (28.2%)	177 (49%)	Ref		Ref	
Reactive hyperglycemia							
Yes	6 (1.9%)	2 (5.1%)	8 (2.2%)	2.85 (0.55–14.62)	0.210	2.97 (0.30–29.78)	0.355
No	316 (98.1%)	37 (94.9%)	353 (97.8%)	Ref		Ref	
Gastrointestinal tract disease							
Yes	136 (42.2%)	18 (46.2%)	154 (42.7%)	1.17 (0.60–2.29)	0.641		
No	186 (57.8%)	21 (53.8%)	207 (57.3%)	Ref			

* Statistically significant at p=0.05
** Statistically significant at p=0.001

Discussion

Antibiotic profile

Levofloxacin was on of the highest DDD in our study. Based on The American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) 2019 and Pneumonia Guidelines of Indonesian Society of Respirology, quinolone monotherapy or a combination of β-lactam and macrolide is recommended to treat community-acquired pneumonia [14,15]. Levofloxacin as the drug of choice was given according to the guideline. Dr. Ramelan Navy Hospital, Indonesia, reported that levofloxacin had the highest DDD/100-patient days prescribed antibiotic used for COVID-19 inpatients. Similar findings were also reported in Dr. R. Koesma Tuban General Hospital, Indonesia, levofloxacin with 83.10 DDD/patient-days [16]. On the contrary, azithromycin had the highest DDD/100-patient days at Diponegoro National Hospital, Indonesia, while levofloxacin placed second in number [17].

Azithromycin was considered the drug of choice to treat COVID-19 during the time. Azithromycin was known for having a better epithelial barrier effect and less arrhythmogenic compared to other macrolides [18]. However, it was only for a short period, as in 2020, WHO suggested putting it on hold, unless bacterial infection was confirmed, as it was not proven to be effective against COVID-19 [1]. A similar azithromycin DDD calculation of 44.54 DDD/100-patient days was reported at Prof. Dr. R. D. Kandou General Hospital (tertiary hospital), Indonesia [19]. Diponegoro National Hospital revealed a higher number of 73.73 DDD/100-patient days among COVID-19 patients [17].

Ceftriaxone's DDD calculation was considered low compared to levofloxacin and azithromycin in this study. Prof. Dr. R. D. Kandou General Hospital and Dr. R. Koesma Tuban General Hospital found similar DDD calculations for ceftriaxone, 17.24 and 17.17, respectively [16, 19]. However, ceftriaxone has not proven to have any benefit for better clinical outcomes for COVID-19 patients [20].

High DDD calculation might suggest that the selected drug is safe, easy to dispense, and available at the health care facility. Conversely, low DDD calculation might imply that the doctor prescribed more selective antibiotics and considered antimicrobial stewardship (AMS), or it could also mean stockouts of medicine [11,21].

Association between antibiotic usage and clinical outcome

The use of antibiotics on COVID-19 patients is controversial, and its efficacy remains uncertain. During the early stages of the pandemic, the immunomodulator effect of antibiotics and prevention of secondary infection was considered an advantage against viral infection. As the specific drug has already been discovered to treat COVID-19, WHO has declared the recommendation to not prescribe antibiotics to mild-moderate symptoms of COVID-19 patients or as prophylaxis [22,23]

Attentive to AMS should be the priority. Overuse and misuse of antibiotics are the main reasons that make antibiotics less effective and might pose a threat in the future. Antibiotic-resistant bacteria are predicted to be the leading cause of death by 2050 and burden the global economy with at least a hundred trillion dollars [2,24,25]

Factor associated with COVID-19 clinical outcome

Despite many literatures stating that age contributes to both the severity and mortality of COVID-19 patients, the age-specific mortality rate varies across countries. One study compared the mortality between patients aged under 50 and those ≥50 years in developing countries. Among the latter, it was found that each 10-year increase after 50 years increased the risk of mortality significantly [26,27]. Another study reported that older age plays an important part in increasing the risk of COVID-19 severity by decreasing the immune system and vital organ capacity [28]. Regardless of health status, patients aged more than 70 years showed a higher mortality risk than younger patients [29]

COVID-19 pathogenesis could trigger a cytokine storm by dysregulating pro-inflammatory cytokine serum. The excessive production of cytokine affects tissue organs and may result in

multi-organ failure and death. Sepsis could be the response to severe infection [30]. Hence, adequate treatment of COVID-19 infection might also treat sepsis [31].

Pneumonia caused by viruses is undistinguishable from bacterial pneumonia unless there is microbial culture confirmation. Poor conditions due to severe viral infection could lead to septic shock and higher mortality rates [32]. A study found that patients with severe pneumonia might have a poor prognosis as more than one-third of the patients died within 72 hours after developing septic shock [33]. Chronic obstructive pulmonary disease (COPD) is also a condition that cannot be neglected. COVID-19 patients with underlying COPD might have at least 6 times increased risk of death [34]. Enforced lockdown during the pandemic significantly reduced the acute exacerbation episode of COPD as it could have been prevented [35].

Conclusion

Our data indicated that use of the antibiotics was prevalent in COVID-19 patients with azithromycin and levofloxacin had the highest DDD. The use of the antibiotics was not associated with the clinical outcome of the COVID-19 patients directly. In contrast, older age and having sepsis or another pulmonary disease had significant association with unfavorable clinical outcomes. Consideration of using antibiotic drugs in COVID-19 should be taken more seriously to manage a better antimicrobial stewardship program, optimize the use of antibiotics, and prevent their unnecessary side effects.

Ethics approval

The Ethics Committee of Dr Zainoel Abidin Hospital has given permission to conduct this study as stated in certificate (No 041/ETIK-RSUDZA/2022). Informed consent was waived in this retrospective study.

Competing interests

The authors declare that there is no conflict of interest.

Acknowledgments

The authors would like to thank you to the Medical Record Database Unit and Microbiology Laboratory at Dr Zainoel Abidin Hospital who provided aid and support in completing this study.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

Yossadania A, Hayati Z, Harapan H, *et al.* Quantity of antibiotic use and its association with clinical outcomes in COVID-19 patients: A snapshot from a provincial referral hospital in Indonesia. Narra J 2023; 3 (3): e272 - http://doi.org/10.52225/narra.v3i3.272.

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