Indonesian Journal of Pharmaceutical Education (e-Journal) 2026; 6 (2):323– 337
ISSN: 2775- 3670 (electronic)
Journal Homepage: http://ejurnal.ung.ac.id/index.php/ijpe/index
DOI: 10.37311/ijpe.v6i2.39488

Rationality of Empirical Antibiotic Prescribing and Its Association with Length of Hospital Stay in Patients with Severe COVID-19

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Article Info:
Received: 4 March 2026
in revised form: 14 July 2026
Accepted: 25 July 2026
Available Online: 31 July 2026

Keywords:
Empirical antibiotic prescribing;
Antibiotic rationality;
Severe-to-critical COVID-19;
Length of hospital stay;
Antimicrobial stewardship

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ABSTRACT

Excessive empirical antibiotic prescribing during the COVID-19 pandemic raised concerns regarding antimicrobial resistance, particularly in hospitals with limited microbiological diagnostic capacity. This study aimed to describe empirical antibiotic prescribing patterns, evaluate the rationality of antibiotic use, and examine its association with length of hospital stay among patients with severe-to-critical COVID-19 at a private secondary-care hospital in Batam City, Indonesia. A retrospective observational study was conducted using the medical records of 120 patients admitted between April and June 2022. Antibiotic rationality was evaluated according to drug selection, dose, route of administration, dosing interval, and treatment duration using the local Hospital Antibiotic Use Guideline, the Indonesian COVID-19 Management Guideline, and relevant international guidelines. Length of stay was compared between patients receiving antivirals with antibiotics and those receiving antivirals without antibiotics, followed by multivariable linear regression. Of the 120 patients, 99 received antibiotics and 21 received no antibiotics. The most frequently prescribed regimen was levofloxacin combined with meropenem (20.83%), followed by levofloxacin monotherapy (18.33%). Among antibiotic recipients, appropriateness was 64.6% for drug selection, 79.8% for dose, 96.0% for route of administration, 94.9% for dosing interval, and 100% for treatment duration. Patients receiving antivirals with antibiotics had a shorter mean length of stay than those receiving antivirals without antibiotics (9.2 ± 2.4 versus 12.8 ± 3.1 days; $p = 0.002$). After adjustment for age, sex, comorbidity, oxygen-support level, and antiviral type, antibiotic co-administration remained associated with a 3.6-day shorter hospital stay (adjusted $\beta = -3.6$; 95% CI, −4.8 to −2.3; $p < 0.001$). However, this association should not be interpreted as evidence of a causal therapeutic benefit because of the retrospective design, residual confounding, informative censoring, and the absence of microbiological confirmation. These findings support strengthening pharmacist-led prescription review, guideline-based antibiotic audits, renal-dose adjustment, and antimicrobial stewardship in hospitals with limited microbiological facilities.

How to cite (APA 6th Style):

Oktaviani,F., & Candra,H. (2026). *Rationality of Empirical Antibiotic Prescribing and Its Association with Length of Hospital Stay in Patients with Severe COVID-19*. *Indonesian Journal of Pharmaceutical Education (e-Journal)*, *6*(2), 323–337.

ABSTRAK

Peresepan antibiotik empiris yang berlebihan selama pandemi COVID-19 menimbulkan kekhawatiran terhadap peningkatan resistensi antimikroba, terutama di rumah sakit dengan keterbatasan fasilitas diagnostik mikrobiologi. Penelitian ini bertujuan menggambarkan pola peresepan antibiotik empiris, mengevaluasi rasionalitas penggunaan antibiotik, dan menganalisis hubungannya dengan lama rawat inap pada pasien COVID-19 berat hingga kritis di sebuah rumah sakit swasta tingkat sekunder di Kota Batam, Indonesia. Penelitian observasional retrospektif dilakukan menggunakan rekam medis 120 pasien yang dirawat pada April–Juni 2022. Rasionalitas penggunaan antibiotik dievaluasi berdasarkan pemilihan obat, dosis, rute pemberian, interval pemberian, dan durasi terapi dengan mengacu pada Panduan Penggunaan Antibiotik rumah sakit, Pedoman Tata Laksana COVID-19 Indonesia, dan pedoman internasional yang relevan. Lama rawat inap dibandingkan antara pasien yang menerima antivirus disertai antibiotik dan pasien yang menerima antivirus tanpa antibiotik, kemudian dianalisis menggunakan regresi linear multivariat. Dari 120 pasien, sebanyak 99 pasien menerima antibiotik dan 21 pasien tidak menerima antibiotik. Regimen yang paling sering digunakan adalah kombinasi levofloksasin dan meropenem (20,83%), diikuti levofloksasin tunggal (18,33%). Pada pasien yang menerima antibiotik, tingkat ketepatan adalah 64,6% untuk pemilihan obat, 79,8% untuk dosis, 96,0% untuk rute pemberian, 94,9% untuk interval pemberian, dan 100% untuk durasi terapi. Pasien yang menerima antivirus disertai antibiotik memiliki rata-rata lama rawat inap lebih pendek dibandingkan pasien yang menerima antivirus tanpa antibiotik (9,2 ± 2,4 dibandingkan 12,8 ± 3,1 hari; p = 0,002). Setelah disesuaikan terhadap usia, jenis kelamin, komorbiditas, tingkat dukungan oksigen, dan jenis antivirus, pemberian antibiotik tetap berhubungan dengan lama rawat inap yang lebih pendek sebesar 3,6 hari (β tersesuaikan = −3,6; IK 95%, −4,8 hingga −2,3; p < 0,001). Namun, hubungan tersebut tidak dapat ditafsirkan sebagai bukti manfaat kausal antibiotik karena desain retrospektif, kemungkinan perancu residual, *informative censoring*, dan tidak tersedianya konfirmasi mikrobiologis. Hasil penelitian ini mendukung penguatan kajian resep oleh apoteker, audit penggunaan antibiotik berbasis pedoman, penyesuaian dosis berdasarkan fungsi ginjal, dan program pengendalian resistensi antimikroba di rumah sakit dengan keterbatasan fasilitas mikrobiologi.

Kata Kunci: Peresepan antibiotik empiris; Rasionalitas antibiotik; COVID-19 berat hingga kritis; Lama rawat inap; Pengendalian resistensi antimikroba

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first reported in Wuhan, China, in late 2019 and was declared a global pandemic by the World Health Organization on 11 March 2020 [1]. Its clinical spectrum ranges from asymptomatic infection to acute respiratory distress syndrome that may progress to multi-organ failure, particularly in patients with comorbidities such as hypertension, diabetes mellitus, and chronic lung disease [2]. In severe COVID-19, alveolar epithelial damage and immune dysregulation predispose patients to secondary bacterial infections, including community-acquired co-infection

and nosocomial superinfections such as hospital-acquired and ventilator-associated pneumonia [3],[4]. To prevent these complications, empirical antibiotic therapy has become a standard component of management for severe disease [5].

Excessive antibiotic prescribing throughout the pandemic has nevertheless raised serious concern. Several studies indicate that more than 70% of hospitalized COVID-19 patients received antibiotics, although the documented prevalence of bacterial co-infection was only 3.5–7% [4],[6]. This pattern has compounded the antimicrobial resistance (AMR) crisis, which the World Health Organization lists among the top ten global health threats [7].

Reports from Indonesian hospitals have identified levofloxacin, ceftriaxone, meropenem, and azithromycin as the antibiotics most commonly prescribed in COVID-19 patients [8], [9]. The expanded use of broad-spectrum agents has contributed to rising resistance among ESKAPE pathogens *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. [10], [11]. To curb these trends, Indonesia has adopted the Antimicrobial Resistance Control Programme (Program Pengendalian Resistensi Antimikroba/PPRA) through Ministry of Health Regulation No. 8/2015, which mandates each hospital to develop a local Antibiotic Use Guideline (Panduan Penggunaan Antibiotik/PPAB) [12].

Internationally, the 2019 IDSA/ATS guideline for community-acquired pneumonia recommends a β-lactam–macrolide combination, or monotherapy with a respiratory fluoroquinolone, for non-intensive-care-unit inpatients, while reserving carbapenems for patients with risk factors for extended-spectrum β-lactamase (ESBL)-producing organisms or *Pseudomonas aeruginosa* [13]. The 2021 IDSA guideline for the treatment and management of patients with COVID-19 further emphasizes that antibiotics should not be routinely administered unless bacterial co-infection is strongly suspected [14]. Auditing empirical prescribing against such evidence-based references is a core element of any antimicrobial stewardship (AMS) programme [15].

In addition to antibiotics, severe COVID-19 patients commonly receive antiviral agents such as remdesivir or favipiravir. Remdesivir has been associated with reduced mortality and shorter hospitalization in patients with moderate-to-severe disease [16], [17]. However, evidence on the association between combined antiviral–antibiotic therapy and length of stay (LOS) in Indonesian settings remains scarce, and previous reports rarely adjust for confounding by indication.

A further limitation of the existing literature is its concentration on tertiary referral hospitals in major metropolitan centres, which typically operate full-service microbiology laboratories. The situation in private secondary-care hospitals, which represent a substantial share of inpatient capacity in Indonesia, has rarely been documented, even though most such facilities operate without on-site bacterial culture and susceptibility services. In this context, antibiotic decision-making depends almost entirely on locally adapted PPAB, clinical syndromes, and regional antibiograms. Evidence on whether PPAB-driven empirical prescribing achieves acceptable rationality, and how it relates to clinical outcomes, is therefore of considerable policy relevance.

Evidence on whether PPAB-driven empirical prescribing achieves acceptable rationality, and how it relates to clinical outcomes in private secondary-care hospitals without on-site microbiology, is scarce, even though these hospitals carry a large share of Indonesian inpatient care. Accordingly, this study aimed to (i) describe empirical antibiotic prescribing in confirmed severe COVID-19 inpatients at such a hospital in Batam City; (ii) evaluate its rationality against an explicit operational matrix anchored on PPAB, the Indonesian COVID-19 Management Guideline, and the IDSA/ATS

guideline; and (iii) examine the unadjusted and adjusted association between antiviral–antibiotic combination therapy and LOS. The novelty of this work lies in auditing antibiotic rationality specifically in a microbiology-limited private secondary-care setting, providing a practical stewardship reference for the many low- and middle-income hospitals that must prescribe empirically without culture support.

2. Materials and Methods

Study Design and Setting

A retrospective, single-centre, observational study with a cross-sectional analytical design was carried out at a private secondary-care hospital in Batam City, Riau Islands Province, Indonesia. Data were extracted from the medical records of patients hospitalized between April and June 2022, the peak period of the Omicron wave in the city. The study hospital provides general inpatient and intensive care services but does not operate an on-site microbiology laboratory; consequently, neither bacterial culture nor antimicrobial susceptibility testing was routinely available. Both empirical and definitive antibiotic prescribing therefore relied on the institution's Hospital Antibiotic Use Guideline (PPAB), which had been adapted from the national PPRA framework and the most recent Indonesian COVID-19 Management Guideline. The absence of an on-site microbiology laboratory is a defining feature of this setting and constitutes a major limitation to be weighed when interpreting antibiotic rationality, because appropriateness could be judged only against guideline concordance rather than against culture-directed therapy.

Ethical Approval

This study was approved by the Health Research Ethics Committee of Universitas Batam (Approval No. 076/LPPM-UNIBA/PI-EC/IV/2022).

Population and Sample

The study population comprised all inpatients with confirmed COVID-19 admitted during the study period. A total sampling method was used, in which every patient who met the predefined criteria was included. Inclusion criteria were (i) a positive reverse transcription polymerase chain reaction (RT-PCR) result for SARS-CoV-2; (ii) classification as severe or critical disease according to the Indonesian COVID-19 Management Guideline issued by the Ministry of Health [5]—severe disease being defined as clinical signs of pneumonia together with a respiratory rate >30 breaths/min, severe respiratory distress, or peripheral oxygen saturation (SpO_2) <93% on room air, and critical disease as acute respiratory distress syndrome, sepsis, or a requirement for mechanical ventilation or vasopressor support; and (iii) availability of complete medical records covering admission, treatment, and discharge. Both severe and critical cases were included and analysed together as the severe-disease group. Exclusion criteria were non-severe (mild or moderate) disease and incomplete records.

Data Collection

A standardized case-report form was used to extract the following information from each medical record: (i) demographic data (age, sex); (ii) comorbidities, expressed both individually and as a binary "any comorbidity" indicator; (iii) clinical severity markers, comprising the highest level of oxygen support administered (room air, low-flow nasal cannula, non-rebreather mask, high-flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation), intensive care unit (ICU) admission, and

survival status at discharge; (iv) baseline laboratory results within 24 hours of admission, including total leukocyte count, C-reactive protein (CRP), and serum creatinine, from which the estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation; (v) antiviral therapy received (remdesivir, favipiravir, or none); (vi) antibiotic therapy received (drug, dose, route, dosing interval, and duration); and (vii) LOS in days, defined as the interval from admission to discharge, death, or transfer.

Operational Definitions of Rationality

Rationality of antibiotic use was assessed across five parameters-drug selection, dose, route of administration, dosing interval, and treatment duration-using criteria derived from the local Hospital Antibiotic Use Guideline (PPAB) of the study site, the national PPAB established by Ministry of Health Regulation No. 8 of 2015 [12], the Indonesian COVID-19 Management Guideline [1],[5], and the 2021 Infectious Diseases Society of America (IDSA) guideline for the treatment and management of patients with COVID-19 [14]. Because the study hospital did not perform bacterial culture, "appropriate drug selection" was operationally defined as concordance with PPAB recommendations for the patient's clinical syndrome (community-acquired pneumonia, hospital-acquired pneumonia, sepsis, or urinary tract infection) rather than concordance with culture-directed therapy. Appropriateness of dose, interval, and route incorporated mandatory adjustment for renal function and the established criteria for intravenous-to-oral switch [18]. Data validity was ensured through independent review by a multidisciplinary team comprising a pulmonologist, an internist, a member of the Hospital Antimicrobial Resistance Control Committee (Panitia Pengendali Resistensi Antibiotik/PPRA), and a clinical pharmacist of the hospital.

The explicit operational criteria used to judge each rationality parameter, together with their reference sources, are summarized in **Table 1**.

Table 1. Operational criteria and reference sources for the assessment of antibiotic-use rationality

Parameter	Criterion for "appropriate"	Criterion for "inappropriate"	Reference source
Drug selection	Regimen matches the PPAB recommendation for the documented clinical syndrome (CAP, HAP, sepsis, or UTI), with the narrowest suitable spectrum; carbapenem used only when ESBL/*Pseudomonas* risk factors are documented.	Regimen does not match the PPAB syndrome recommendation, or empirical carbapenem used without documented ESBL/*Pseudomonas* risk.	Local PPAB; national PPRA (PMK No. 8/2015); IDSA/ATS CAP guideline (2019); IDSA COVID-19 guideline (2021)
Dose	Within the PPAB/reference range and adjusted for renal function (eGFR) where needed (e.g., meropenem 1 g every 12 h at eGFR <60).	Outside the recommended range, or not adjusted for reduced eGFR.	Local PPAB; renal-dosing references
Route of administration	Matches disease severity; IV-to-oral switch applied once switch criteria are met.	IV therapy continued after the patient meets IV-to-oral switch criteria.	Local PPAB; IV-to-oral switch criteria

Parameter	Criterion for "appropriate"	Criterion for "inappropriate"	Reference source
Dosing interval	Follows the reference and is extended in renal impairment where needed (e.g., levofloxacin every 48 h).	Interval not extended in renal impairment.	Local PPAB; renal-dosing references
Treatment duration	Within the recommended course (5–7 days uncomplicated; 10–14 days complicated) and stopped at clinical stability.	Shorter or longer than the recommended course.	Local PPAB; IDSA/ATS CAP guideline (2019)

CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; UTI = urinary tract infection; ESBL = extended-spectrum β-lactamase; eGFR = estimated glomerular filtration rate.

Statistical Analysis

Continuous variables were tested for normality using the Shapiro–Wilk test and for homogeneity of variance using Levene's test. Normally distributed variables are presented as mean ± standard deviation and were compared with an independent-samples t-test; non-normally distributed variables are presented as median (interquartile range, IQR) and were compared with the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. The magnitude of group differences in LOS was quantified using Cohen's d, with values of 0.2, 0.5, and 0.8 interpreted as small, medium, and large effects, respectively[19].

To adjust for confounding by indication, multivariable linear regression was used to model LOS as the dependent variable. Independent variables comprised the antibiotic-treatment group (combined antiviral–antibiotic vs antiviral monotherapy), age, sex, the presence of any comorbidity, the highest level of oxygen support during admission (categorized as low-flow vs high-flow/non-invasive vs invasive ventilation), and antiviral type. C-reactive protein, leukocyte count, eGFR, ICU admission, and in-hospital mortality were used for descriptive comparison between the treatment groups (Table 3) and were not entered as predictors in the regression model, in order to avoid over-fitting given the available sample size. Effect estimates are reported as adjusted β-coefficients with 95% confidence intervals (CI). The assumptions of linearity, independence, homoscedasticity, and normality of residuals were examined and were acceptable; the highest variance inflation factor was 1.11 (all <5), indicating no problematic multicollinearity, and the model explained an adjusted R^2 of 0.199 (19.9% of the variance in LOS). All tests were two-tailed with a significance threshold of $p < 0.05$. Analyses were performed in IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA).

3. Results and Discussion

Patient Characteristics

A total of 120 patients met all inclusion criteria and were included in the final analysis. Their demographic, comorbidity, and clinical severity characteristics are shown in **Table 2**. Male patients constituted a slight majority (54.17%), and 70.0% of the cohort was older than 46 years. Hypertension (27.50%) and diabetes mellitus (23.33%) were the most frequent comorbidities, in agreement with earlier Indonesian reports on severe COVID-19 [8],[9]. The male predominance is consistent with biological hypotheses linking sex-specific differences in angiotensin-converting enzyme 2 (ACE2) expression and the relative immunoprotective effect of oestrogen to clinical severity [20],[21]. Disease severity in the cohort was substantial: 45.83% of patients required high-flow

nasal cannula or higher levels of respiratory support, 29.17% were admitted to the ICU, 18.33% had an eGFR below 60 mL/min/1.73 m², and the in-hospital mortality rate reached 15.00%. The high baseline CRP above 100 mg/L in 70.83% of patients reflects the intense inflammatory state of severe COVID-19 but is not pathognomonic of bacterial co-infection, since marked CRP elevation also occurs as part of the viral cytokine response [22].

Table 2. Characteristics of patients with confirmed severe COVID-19 (n = 120)

Characteristic	Category	n	%
Sex	Male	65	54.17
	Female	55	45.83
Age (years)	18–30	11	9.17
	31–45	25	20.83
	46–60	49	40.83
	>60	35	29.17
Comorbidity	Hypertension	33	27.50
	Diabetes mellitus	28	23.33
	Asthma	8	6.67
	COPD	6	5.00
	Hypertension + CKD	6	5.00
	No comorbidity	39	32.50
Highest oxygen support	Low-flow nasal cannula	25	20.83
	Non-rebreather mask	40	33.33
	High-flow nasal cannula	30	25.00
	Non-invasive ventilation	15	12.50
	Invasive mechanical ventilation	10	8.33
ICU admission	Yes	35	29.17
In-hospital mortality	Yes	18	15.00
eGFR (mL/min/1.73 m²)	<60	22	18.33
Baseline CRP (mg/L)	>100	85	70.83
Baseline WBC (×10³/µL)	>12	30	25.00
LOS (days)	Median (IQR)	10 (8–13)	–

Note: ICU = intensive care unit; eGFR = estimated glomerular filtration rate; CRP = C-reactive protein; WBC = white blood cell; IQR = interquartile range; LOS = length of stay; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease.

The relevance of age and comorbidity for antibiotic prescribing extends beyond simple risk stratification. Immunosenescence and the chronic inflammatory state of metabolic disease alter both infection risk and pharmacokinetics [23]. Hypertension upregulates ACE2 expression, providing additional cellular entry points for SARS-CoV-2, while chronic hyperglycaemia in diabetes impairs innate and adaptive immune responses [23]. Coexistent chronic kidney disease—present in 5.00% of the cohort, with a further proportion meeting the eGFR threshold—has direct implications for renally cleared agents such as meropenem and levofloxacin, mandating dose and interval adjustment to avoid toxicity or therapeutic failure.

Baseline characteristics compared between the combined antiviral–antibiotic group and the antiviral-monotherapy (no-antibiotic) group-including in-hospital mortality in each group-are shown in **Table 3**.

Table 3. Baseline characteristics by treatment group

Characteristic	Combined antiviral–antibiotic (n = 99)	Antiviral monotherapy / no antibiotic (n = 21)	p-value
Age, years, mean ± SD	54.2 ± 17.8	52.4 ± 15.9	0.673
Male sex, n (%)	52 (52.5)	13 (61.9)	0.478
Any comorbidity, n (%)	70 (70.7)	11 (52.4)	0.126
High-flow/non-invasive/invasive oxygen support, n (%)	45 (45.5)	10 (47.6)	1.000
ICU admission, n (%)	28 (28.3)	7 (33.3)	0.792
In-hospital mortality, n (%)	13 (13.1)	5 (23.8)	0.309
Baseline CRP >100 mg/L, n (%)	70 (70.7)	15 (71.4)	1.000
Baseline WBC >12 $\times 10^3/\mu L$, n (%)	23 (23.2)	7 (33.3)	0.406
eGFR <60 mL/min/1.73 m^2, n (%)	21 (21.2)	1 (4.8)	0.118
Remdesivir (vs favipiravir), n (%)	57 (57.6)	13 (61.9)	0.810

Age was compared with the independent-samples t-test; categorical variables were compared with the chi-square or Fisher's exact test, as appropriate. CRP = C-reactive protein; WBC = white blood cell; ICU = intensive care unit; eGFR = estimated glomerular filtration rate; SD = standard deviation.

Pattern of Antiviral and Antibiotic Use

The distribution of antiviral therapy is summarized in **Table 4**. Remdesivir was the dominant antiviral agent (58.33%), in keeping with the recommendations of the World Health Organization and the Indonesian COVID-19 Management Guideline for moderate-to-severe COVID-19 patients requiring supplemental oxygen[1], [16]. As a nucleotide analogue, remdesivir inhibits the RNA-dependent RNA polymerase of SARS-CoV-2 and was shown in the ACTT-1 trial to shorten recovery time among hospitalized patients requiring oxygen support [16]. Favipiravir was used in 41.67% of patients, mainly in those without intravenous access or with lower oxygen demand, and has also been associated with shorter LOS in Indonesian COVID-19 inpatients[24].

Table 4. Pattern of antiviral use (n = 120)

Type of antiviral	n	%
Remdesivir injection	70	58.33
Favipiravir tablet	50	41.67

The pattern of antibiotic prescribing is shown in **Table 5**. The levofloxacin–meropenem combination was the most frequent regimen (21%), followed by levofloxacin alone (18%) and the choice of no antibiotic (18%).

Table 5. Pattern of antibiotic use (n = 120)

Type of antibiotic	Drug class	n	%
Levofloxacin + Meropenem inj.	Fluoroquinolone + Carbapenem	25	20.83
Levofloxacin inj.	Fluoroquinolone	22	18.33
No antibiotic	—	21	17.50

Levofloxacin + Azithromycin	Fluoroquinolone + Macrolide	16	13.33
Ceftizoxime inj.	Third-generation cephalosporin	14	11.67
Meropenem inj.	Carbapenem	12	10.00
Ceftriaxone + Azithromycin	Cephalosporin + Macrolide	6	5.00
Azithromycin tab.	Macrolide	4	3.33

Note: inj. = injection; tab. = tablet. The "no antibiotic" group (n = 21, 17.50%) is the same group as the antiviral-monotherapy arm used in the length-of-stay comparison (Table 8).

Broad-spectrum agents therefore accounted for most prescriptions, mirroring patterns reported by Limato et al. [9] in Indonesian national referral hospitals. The high reliance on carbapenems is of particular concern because the World Health Organization AWaRe classification places carbapenems in the "Watch" category, with use restricted to defined indications [7]. Uncontrolled use is known to drive the emergence of carbapenemase-producing Enterobacteriaceae, a recognized threat in Indonesian tertiary settings[11]. Levofloxacin and third-generation cephalosporins, by contrast, are aligned with first-line empirical recommendations of the 2019 IDSA/ATS guideline for community-acquired pneumonia[13]. The 18% of patients managed without antibiotics suggests that a subset of clinicians applied prudent prescribing, in keeping with AMS principles[15].

Rationality of Antibiotic Use

Among the 99 patients who received antibiotics, the rationality profile is presented in **Table 6**. Appropriateness was lowest for drug selection (64.6%) and dose (79.8%), and highest for treatment duration (100%). Route (96.0%) and interval (94.9%) were also acceptable. The 35.4% rate of inappropriate drug selection (35 of 99 courses) was driven entirely by the empirical use of carbapenems without documented ESBL or *Pseudomonas* risk factors. Because the study hospital had no microbiology laboratory, the assessment of "appropriate selection" relied on documented clinical and epidemiological risk factors recorded in the medical record. Without microbiological confirmation, even a PPAB-compliant decision cannot be downgraded to a culture-targeted regimen, which underscores a structural limitation of stewardship in such settings rather than an individual clinician failure [15]. Meropenem-containing regimens accounted for 37 of the 99 antibiotic courses (levofloxacin–meropenem, n = 25; meropenem monotherapy, n = 12); of these, 35 were classified as inappropriate drug selection because meropenem had been started empirically in patients without any documented risk factor for ESBL-producing Enterobacterales or Pseudomonas aeruginosa, contrary to the reservation criteria of the local PPAB and the 2019 IDSA/ATS guideline [13].

Table 6. Appropriateness of antibiotic use (n = 99)

Parameter	Appropriate, n (%)	Inappropriate, n (%)	Basis of inappropriate cases
Drug selection	64 (64.6)	35 (35.4)	Empirical carbapenem prescribed without documented ESBL/Pseudomonas risk factor
Dose	79 (79.8)	20 (20.2)	Meropenem/levofloxacin not adjusted for reduced renal function (eGFR <60)
Route of administration	95 (96.0)	4 (4.0)	Intravenous therapy continued despite meeting IV-to-oral switch criteria
Dosing interval	94 (94.9)	5 (5.1)	Levofloxacin dosing interval not extended to 48 h in renal impairment
Treatment duration	99 (100)	0 (0)	—

Inappropriate dosing (20.2%) occurred primarily in patients with reduced renal function (eGFR <60 mL/min/1.73 m²), in whom meropenem and levofloxacin doses were not adjusted as required by PPAB (**Table 7**). Subtherapeutic concentrations risk both treatment failure and resistance, whereas supratherapeutic concentrations increase the risk of nephrotoxicity, neurotoxicity, and QT-interval prolongation. Standardized pharmacist-led dose review—an established core element of AMS programmes—remains the most feasible intervention to address this gap [15].

Table 7. Antibiotics not adjusted to renal function among patients with eGFR <60 mL/min/1.73 m²

Antibiotic	Patients with eGFR <60 receiving the drug, n	Not dose-adjusted, n (%)	Adjustment required per PPAB
Meropenem	8	8 (100.0)	Reduce dose and/or extend interval when eGFR <60 (e.g., 1 g every 12 h; further reduction if eGFR <25)
Levofloxacin	19	19 (100.0)	Reduce dose and extend interval when eGFR <50 (e.g., 750 mg then 750 mg every 48 h)
Other renally cleared agent (ceftizoxime)	1	0 (0.0)	Adjust dose/interval per renal-dosing references

Percentages are relative to the number of patients receiving each drug; patients on the levofloxacin + meropenem combination are counted in both drug rows. eGFR = estimated glomerular filtration rate; PPAB = Hospital Antibiotic Use Guideline.

Inappropriate route (4%) involved patients who met the intravenous-to-oral switch criteria specified by PPAB (clinical improvement, ability to tolerate oral intake, haemodynamic stability) but continued to receive intravenous therapy. Timely switch shortens intravenous exposure, reduces phlebitis and catheter-related infection, and supports earlier discharge [18]. Inappropriate interval (5%) occurred entirely in chronic kidney disease patients for whom the levofloxacin interval should have been extended to every 48 hours. The 100% appropriateness of duration reflects strong adherence to the PPAB recommendation of 5–7 days for uncomplicated pneumonia and 10–14 days for complicated infections—a finding consistent with the 2019 IDSA/ATS recommendation that therapy be discontinued once clinical stability is achieved [13],[15].

Procalcitonin testing, which has emerged as a useful adjunct for guiding antibiotic initiation and de-escalation in respiratory tract infections[22], is not routinely available at the study hospital. In its absence, empirical broad-spectrum prescribing may be over-used because clinicians lack a rapid biomarker to differentiate viral pneumonia from bacterial co-infection. Implementation of inflammatory biomarker panels, even when full bacterial culture is unavailable, may therefore represent a high-yield AMS intervention for hospitals operating in this context.

Length of Hospital Stay

LOS comparisons between patients receiving combined antiviral–antibiotic therapy and those receiving antiviral monotherapy are presented in **Table 8**.

Table 8. Unadjusted and adjusted comparison of length of stay by treatment group

Parameter	Combined (n = 99)	Monotherapy (n = 21)	Estimate (95% CI)	p-value
LOS, mean ± SD (days)	9.2 ± 2.4	12.8 ± 3.1	−3.6 (−4.9, −2.3)	0.002
LOS, median (IQR) (days)	9 (8–11)	13 (11–15)	—	<0.001
Effect size, Cohen's d			1.35 (large)	—
Adjusted β-coefficient			−3.6 (−4.8, −2.3)	<0.001

Note: p = 0.002 (mean) is from the independent-samples t-test and p <0.001 (median) from the Mann–Whitney U test; both are reported because LOS deviated modestly from normality. The adjusted β (−3.6 days) is from multivariable linear regression adjusted for age, sex, comorbidity, oxygen support level, and antiviral type. CI = confidence interval; IQR = interquartile range; LOS = length of stay; SD = standard deviation.

The combined therapy group had a shorter unadjusted LOS than the antiviral-monotherapy group (mean 9.2 ± 2.4 vs 12.8 ± 3.1 days; mean difference −3.6 days, 95% CI −4.9 to −2.3; p = 0.002, independent-samples t-test). Because LOS in both groups deviated modestly from normality on Shapiro–Wilk testing, the median (IQR) comparison was added and the Mann–Whitney U test confirmed the difference (9 days [IQR 8–11] vs 13 days [IQR 11–15]; p <0.001). The standardized effect size (Cohen's d = 1.35) was large [19]. After adjustment for age, sex, comorbidity, oxygen support level, and antiviral type, antibiotic co-administration remained associated with a 3.6-day shorter LOS (95% CI −4.8 to −2.3; p <0.001). Because LOS was censored at discharge, death, or transfer, a shorter stay may partly reflect early in-hospital death rather than clinical improvement; in-hospital mortality by treatment group is therefore reported in Table 3, and a sensitivity analysis restricted to survivors was performed, in which the association between antibiotic co-administration and shorter LOS remained statistically significant (adjusted β = −3.2 days; 95% CI −4.6 to −1.7; p <0.001). This result should be interpreted as a statistical association only and not as evidence that antibiotics shorten hospital stay.

These results should be interpreted with caution. The retrospective cross-sectional design cannot establish causality: antibiotic co-administration is not randomly allocated but reflects the clinician's estimate of bacterial co-infection risk, which is itself shaped by oxygen requirement, inflammatory markers, age, and comorbidity[25]. Even after multivariable adjustment, residual confounding by indication, by severity not captured in the chart, and by individual prescriber preference remains plausible. Future work using propensity-score methods or, ideally, prospective designs is needed to clarify whether the association is causal[26].

A second concern is the absence of microbiological confirmation. In the present cohort, neither bacterial co-infection nor bacterial clearance could be objectively

documented. Several large multicentre studies have shown that confirmed bacterial co-infection in hospitalized COVID-19 patients is uncommon (3.5–7%)[4], [6], so a substantial share of empirical antibiotic prescriptions may have been administered to patients without genuine bacterial infection. In that scenario, the apparent LOS benefit could reflect resolution of viral pneumonia rather than antibacterial activity. The observed association should therefore be framed as suggestive rather than confirmatory, and the discussion of mechanism—antibiotics treating bacterial co-infection while antivirals suppress viral replication[3], [27] - must remain hypothetical pending microbiologically anchored evidence.

The implications for AMS in private secondary-care hospitals without microbiology services are nonetheless important. First, a structured PPAB, regularly updated against the IDSA/ATS and national guidelines, can deliver acceptable rationality scores across most parameters, as shown by the >90% appropriateness for route, interval, and duration in this study. Second, the residual gap in drug selection and dose adjustment is addressable through pharmacist-led prescription review, which remains the most consistently effective AMS intervention[15]. Third, even modest investments in adjunctive biomarkers such as procalcitonin and CRP-trend monitoring could enable safer empirical de-escalation in settings where culture is unavailable[22], [28]. Strengthening these elements-rather than mandating culture confirmation that hospitals cannot deliver-is a realistic path to AMS impact in the Indonesian secondary-care network.

Several limitations should be acknowledged. First, the single-centre retrospective design restricts external validity and precludes causal inference. Second, the study hospital does not operate a microbiology laboratory; bacterial culture and antimicrobial susceptibility data were therefore unavailable, and both empirical and definitive antibiotic decisions relied entirely on PPAB. The rationality assessment should consequently be understood as concordance with guideline criteria rather than agreement with culture-directed therapy. Third, although the multivariable model adjusted for the principal clinical drivers of LOS, residual confounding by indication remains plausible. Fourth, adjunctive biomarkers such as procalcitonin were not consistently available, limiting the ability to discriminate viral from bacterial inflammation. Future multicentre studies, ideally with propensity-score matching or prospective enrolment and structured biomarker collection, are warranted to confirm and extend the present findings. In addition, because LOS was censored at discharge, death, or transfer, early in-hospital death could shorten LOS independently of any clinical benefit (informative censoring); the mortality-by-group data (**Table 3**) and the survivor-only sensitivity analysis are reported specifically to make this potential bias explicit, and the LOS finding is therefore presented as an association only.

4. Conclusion

In this cross-sectional study of 120 patients with confirmed severe COVID-19 hospitalized at a private hospital in Batam City, empirical antibiotic prescribing was dominated by broad-spectrum regimens, with the levofloxacin–meropenem combination as the most frequent. Against an operational matrix derived from PPAB, the national COVID-19 Management Guideline, and the IDSA/ATS pneumonia guideline, appropriateness was lowest for drug selection (64.6%) and dose (79.8%) and highest for treatment duration (100%). Combined antiviral–antibiotic therapy was associated with a shorter LOS than antiviral monotherapy, with an adjusted difference

of 3.6 days; this is an association only and must not be read as evidence of a causal effect, because confounding by indication, informative censoring by early death, and the absence of microbiological confirmation cannot be excluded. Accordingly, these findings do not support the routine empirical use of antibiotics in severe COVID-19; antibiotics should be reserved for patients with a genuine clinical suspicion of bacterial co-infection. For private secondary-care hospitals operating without on-site microbiology services, the most realistic stewardship priorities are pharmacist-led prescription review, structured PPAB-anchored audits, and the implementation of inflammatory biomarker panels to support empirical de-escalation. These findings contribute to the growing literature on antimicrobial stewardship implementation in resource-limited hospital settings and provide a practical reference for similar institutions in Indonesia and other low- and middle-income countries.

Acknowledgements:
The authors thank the Directorate General of Higher Education, Research, and Technology (Ditjen Diktiristek), Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia, for funding support through the 2022 Dikti Research Grant. The authors also thank the director and medical-record staff of the private hospital in Batam City for granting access and facilities, and Universitas Batam for its administrative and academic support throughout the study.

Conflict of Interest:
The authors declare no conflict of interest regarding the publication of this paper.

References

[1] F. Isbaniah and A. D. Susanto, "Pneumonia coronavirus disease 2019 (COVID-19)," *Journal of the Indonesian Medical Association*, vol. 70, no. 4, pp. 87–94, 2020. [Online]. Available: https://doi.org/10.47830/jinma-vol.70.4-2020-235

[2] V. Bajaj, N. Gadi, A. P. Spihlman, S. C. Wu, C. H. Choi, and V. R. Moulton, "Aging, immunity, and COVID-19: How age influences the host immune response to coronavirus infections," *Frontiers in Physiology*, vol. 11, art. no. 571416, 2021. [Online]. Available: https://doi.org/10.3389/fphys.2020.571416

[3] Z. Karami *et al.*, "Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID-19: Results from a multicentre retrospective cohort study in the Netherlands," *Infectious Diseases*, vol. 53, no. 2, pp. 102–110, 2021. [Online]. Available: https://doi.org/10.1080/23744235.2020.1839672

[4] B. J. Langford *et al.*, "Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis," *Clinical Microbiology and Infection*, vol. 26, no. 12, pp. 1622–1629, 2020. [Online]. Available: https://doi.org/10.1016/j.cmi.2020.07.016

[5] Ministry of Health of the Republic of Indonesia, *Decree of the Minister of Health of the Republic of Indonesia No. HK.01.07/MENKES/5671/2021 on Clinical Management of Coronavirus Disease 2019 (COVID-19) in Health Care Facilities*. Jakarta, Indonesia: Ministry of Health of the Republic of Indonesia, 2021. [Online]. Available: https://peraturan.bpk.go.id/Details/171647/keputusan-menkes-no-hk0107menkes56712021

[6] L. Lansbury, B. Lim, V. Baskaran, and W. S. Lim, "Co-infections in people with COVID-19: A systematic review and meta-analysis," *Journal of Infection*, vol. 81,

no. 2, pp. 266–275, 2020. [Online]. Available: https://doi.org/10.1016/j.jinf.2020.05.046

[7] World Health Organization, *2021 AWaRe Classification*. Geneva, Switzerland: World Health Organization, 2021. [Online]. Available: https://www.who.int/publications/i/item/2021-aware-classification

[8] R. Limato *et al.*, "Optimizing antibiotic use in Indonesia: A systematic review and evidence synthesis to inform opportunities for intervention," *medRxiv*, 2022. [Online]. Available: https://doi.org/10.1101/2022.02.20.22271261

[9] L. Herliyana, A. Purnamayanti, and F. O. H. Prasetyadi, "Delivering a birth safely: Case reports of perineal infection prevention among pregnant women living around ex-landfills," *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, vol. 9, no. 2, pp. 131–137, 2022. [Online]. Available: https://doi.org/10.20473/jfiki.v9i22022.131-137

[10] A. Dahesihdewi and Y. N. Fanani, "SG-APSIC1074: Trend of 'ESKAPE' and their susceptibility changes for meropenem and levofloxacin during the pandemic at Sardjito Hospital, Yogyakarta, Indonesia," *Antimicrobial Stewardship & Healthcare Epidemiology*, vol. 3, suppl. 1, 2023. [Online]. Available: https://doi.org/10.1017/ash.2023.7

[11] Y. R. Saharman, A. Karuniawati, J. A. Severin, and H. A. Verbrugh, "Infections and antimicrobial resistance in intensive care units in lower-middle income countries: A scoping review," *Antimicrobial Resistance & Infection Control*, vol. 10, art. no. 22, 2021. [Online]. Available: https://doi.org/10.1186/s13756-020-00871-x

[12] Ministry of Health of the Republic of Indonesia, *Regulation of the Minister of Health of the Republic of Indonesia No. 8 of 2015 on the Antimicrobial Resistance Control Program in Hospitals*. Jakarta, Indonesia: Ministry of Health of the Republic of Indonesia, 2015. [Online]. Available: https://farmalkes.kemkes.go.id/unduh/permenkes-8-2015/

[13] J. P. Metlay *et al.*, "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 Journal of Respiratory and Critical Care Medicine*, vol. 200, no. 7, pp. e45–e67, 2019. [Online]. Available: https://doi.org/10.1164/rccm.201908-1581ST

[14] A. Bhimraj *et al.*, "Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19," *Clinical Infectious Diseases*, vol. 78, no. 7, pp. e250–e349, 2024. [Online]. Available: https://doi.org/10.1093/cid/ciae121

[15] M. S. Pulia *et al.*, "National trends in antibiotic prescribing for adults hospitalized with coronavirus disease 2019 and other viral respiratory infections," *Open Forum Infectious Diseases*, vol. 12, no. 2, art. no. ofaf045, 2025. [Online]. Available: https://doi.org/10.1093/ofid/ofaf045

[16] J. H. Beigel *et al.*, "Remdesivir for the treatment of Covid-19: Final report," *The New England Journal of Medicine*, vol. 383, no. 19, pp. 1813–1826, 2020. [Online]. Available: https://doi.org/10.1056/NEJMoa2007764

[17] World Health Organization, *Therapeutics and COVID-19: Living Guideline, August 2025*. Geneva, Switzerland: World Health Organization, 2025. [Online]. Available: https://www.who.int/publications/i/item/B09540

[18] K. McCarthy, "Oral or intravenous antibiotics?," *Australian Prescriber*, vol. 43, no.

2, pp. 45–48, 2020. [Online]. Available: https://doi.org/10.18773/austprescr.2020.008

[19] D. C. Funder and D. J. Ozer, "Evaluating effect size in psychological research: Sense and nonsense," *Advances in Methods and Practices in Psychological Science*, vol. 2, no. 2, pp. 156–168, 2019. [Online]. Available: https://doi.org/10.1177/2515245919847202

[20] G. M. Bwire, "Coronavirus: Why men are more vulnerable to COVID-19 than women?," *SN Comprehensive Clinical Medicine*, vol. 2, pp. 874–876, 2020. [Online]. Available: https://doi.org/10.1007/s42399-020-00341-w

[21] A. Pradhan and C. Olsson, "Sex differences in severity and mortality from COVID-19: Are males more vulnerable?," *Biology of Sex Differences*, vol. 11, art. no. 53, 2020. [Online]. Available: https://doi.org/10.1186/s13293-020-00330-7

[22] N. J. Atallah *et al.*, "Baseline procalcitonin as a predictor of bacterial infection and clinical outcomes in COVID-19: A case-control study," *PLOS ONE*, vol. 17, no. 1, art. no. e0262342, 2022. [Online]. Available: https://doi.org/10.1371/journal.pone.0262342

[23] J. H. Bae, "COVID-19 and diabetes mellitus: From pathophysiology to clinical management," *Nature Reviews Endocrinology*, vol. 17, pp. 11–30, 2021. [Online]. Available: https://doi.org/10.1038/s41574-020-00435-4

[24] A. Asyriva *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*, vol. 3, no. 3, art. no. e272, 2023. [Online]. Available: https://doi.org/10.52225/narra.v3i3.272

[25] T. J. VanderWeele, "Principles of confounder selection," *European Journal of Epidemiology*, vol. 34, pp. 211–219, 2019. [Online]. Available: https://doi.org/10.1007/s10654-019-00494-6

[26] R. J. Desai and J. M. Franklin, "Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: A primer for practitioners," *BMJ*, vol. 367, art. no. l5657, 2019. [Online]. Available: https://doi.org/10.1136/bmj.l5657

[27] T. P. Asmarawati *et al.*, "The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in Indonesia," *F1000Research*, vol. 10, art. no. 113, 2025. [Online]. Available: https://doi.org/10.12688/f1000research.31645.2

[28] C. Michailides *et al.*, "Impact of bacterial infections on COVID-19 patients: Is timing important?," *Antibiotics*, vol. 12, no. 2, art. no. 379, 2023. [Online]. Available: https://doi.org/10.3390/antibiotics12020379