FAKULTAS FARMASI
UNIVERSITAS MUHAMMADIYAH PURWOKERTO

PHARMACY: Jurnal Farmasi Indonesia
(*Pharmaceutical Journal of Indonesia*)

Journal homepage: https://jurnalnasional.ump.ac.id/index.php/PHARMACY

Received 22-05-2025 Accepted 12-12-2025 Available online 31-12-2025

Evaluasi Penggunaan Antibiotik Definitif pada Pasien dengan Infeksi Bakteri Resisten Carbapenem di RSUP Dr. Sardjito, Yogyakarta

Evaluation of Definitive Antibiotic Use in Patients with Carbapenem-Resistant Bacterial Infections at Dr. Sardjito Hospital, Yogyakarta

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A R T I K E L I N F O

Kata Kunci:
Carbapenem-resistant bacteria, clinical outcome, definitive antibiotics, evaluation

A B S T R A K

Currently, many countries have reported infections caused by carbapenem-resistant bacteria, and Indonesia is no exception. This condition makes the scope of therapeutic options becomes quite limited. This study aims to evaluate the definitive antibiotics used in patients with carbapenem-resistant bacterial infections along with the calculation of the predictive value of pharmacokinetic parameters which are then linked to the patient's clinical outcome. This research is a retrospective descriptive-analytic study. The subjects of this study were all inpatients with carbapenem-resistant bacterial infections in the period January-March 2020. Antibiotic suitability evaluation was analyzed descriptively, the estimated values of pharmacokinetic parameters were calculated using the pharmacokinetic calculation formula, and the correlation between the estimated pharmacokinetic values and clinical outcomes of the patients was analyzed statistically using Fisher test. The results of the evaluation of definitive antibiotic administration in patients with carbapenem-resistant bacterial infections found that 11 antibiotics met the suitability of the type, dose, frequency, and duration of the 27 antibiotics analyzed. The predicted value of the pharmacokinetic parameters of the 11 definitive antibiotics in the form of minimal levels in the blood at steady state compared to the MIC value showed that 1 (9.1%) antibiotic had a Css_{min} value ≥ MIC and 10 (90.9%) other antibiotics had a Css_{min} value < MIC. There is no relationship between the predictive value of the pharmacokinetic parameters of definitive antibiotics that meet regimen suitability and clinical outcomes in patients with carbapenem-resistant bacterial infections. In general, although the dosage regimen of definitive antibiotics meet the suitability criteria, drug concentration in blood can be inadequate to eradicate the bacteria due to many factors and can influence the clinical outcomes.

Keywords:
Antibiotik definitive, bakteri resisten karbapenem, evaluasi, luaran klinis

A B S T R A C T

Resistensi bakteri terhadap antibiotik golongan karbapenem menjadi salah satu perhatian khusus saat ini. Banyak negara telah melaporkan banyaknya kasus infeksi yang disebabkan oleh bakteri resisten karbapenem, tak terkecuali Indonesia. Sejak ditemukannya bakteri yang telah resisten terhadap karbapenem menjadikan cakupan pilihan terapi cukup terbatas. Selama belum ditemukannya antibiotik baru, terapi dilakukan dengan memberikan antibiotik empiris atau antibiotik definitif yang sesuai dengan hasil uji sensitivitas antibiotik. Penelitian ini bertujuan untuk melakukan evaluasi terhadap antibiotik definitif yang digunakan pada pasien dengan infeksi bakteri resisten karbapenem beserta perhitungan prediksi nilai parameter farmakokinetik yang selanjutnya dihubungkan dengan luaran klinis pasien. Penelitian ini adalah studi retrospektif deskriptif-analitik. Subjek penelitian ini adalah semua pasien rawat inap dengan infeksi bakteri resisten karbapenem pada periode Januari-Maret 2020. Evaluasi kesesuaian antibiotik dianalisis secara deskriptif, nilai perkiraan parameter farmakokinetik dihitung dengan menggunakan rumus perhitungan farmakokinetik, dan hubungan antara nilai perkiraan farmakokinetik dengan luaran klinis pasien dianalisis secara statistik menggunakan uji Fischer. Hasil evaluasi kesesuaian antibiotik definitif pada pasien dengan infeksi bakeri resisten karbapenem terdapat 11 antibiotik yang memenuhi kesesuaian jenis, dosis, frekuensi, dan durasi dari 27 antibiotik yang dianalisis. Nilai prediksi parameter farmakokinetik dari 11 antibiotik definitif berupa kadar minimal dalam darah pada kondisi tunak yang dibandingkan dengan nilai MIC diperoleh hasil 1 (9,10%) antibiotik memiliki nilai Css_{min} ≥ MIC dan 10 (90,90%) antibiotik lainnya memiliki nilai Css_{min} < MIC. Tidak terdapat hubungan antara nilai prediksi parameter farmakokinetik antibiotik definitif yang memenuhi kesesuaian regimen dengan luaran klinis pada pasien dengan infeksi bakteri resisten karbapenem.

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1. Introduction

Antibiotics are the main therapy used to cure an infectious disease caused by bacteria. The use of antibiotics itself requires special attention to prevent resistance. One class of antibiotics that is widely considered for use is carbapenem. Carbapenem is a class of antibiotic which used when other class antibiotics have experienced resistance. In addition, this class of antibiotics is the most potent antibiotic with proven efficacy as therapy in patients with severe infections (Brunton et al., 2018).

Carbapenem is known to be used more as a definitive antibiotic than as an empirical antibiotic. However, since the early 1990s, carbapenem-resistant bacteria have been reported in Japan and Italy. The outbreak of antimicrobial resistance cause a great threat fort the health of human and also animals (Li et al., 2017). Thus, in 2017, WHO released a list of pathogens that require the development and discovery of new antibiotics. WHO divides into three categories that indicate the level of priority, namely critical, high, and medium. Carbapenem-resistant bacterias are included in the critical category. The groups of bacteria included in it are *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacterales. The publication of Guh et al. in 2014 stated that carbapenem-resistant bacteria are also resistant to most other classes of antibiotics (Guh et al., 2014). Thus, therapeutic options become more limited. As a result, mortality and morbidity rates due to infectious diseases are increasing. Similarly, the cost of care and the length of hospitalization are also increasing (Lemos et al., 2014; Liu et al., 2015; Prakobsrikul et al., 2019).

Knowing the risks that occur due to the increasing findings of carbapenem-resistant bacteria, many countries in the world have reported the prevalence of carbapenem-resistant bacteria. In Dr. Sardjito Hospital Yogyakarta, Indonesia, the prevalence of carbapenem-resistant bacteria showed a high percentage in the January-August 2020 period. The percentage of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* bacteria were 46.43%-70% and 12.82%-23.33%, respectively. Meanwhile, in the Enterobacterales bacteria group (*Klebsiella pneumoniae* and *Escherichia coli*) the prevalence rate was 0.73%-8.24% (Primasari et al., 2022).

Related to the use of antibiotics in infectious patients, there have been many studies on the evaluation of antibiotic suitability. One of them is a study conducted by Nuryah et al in 2019, regarding the evaluation of the suitability of antibiotic use in patients with Methicillin Resistant *Staphylococcus aureus* (MRSA) infection at Dr. Soeradji Tirtonegoro Klaten General Hospital (Nuryah et al., 2019). In this study, it was found that there was no significant relationship between the use of antibiotics and the clinical outcomes of patients with MRSA infection. Similar research was also conducted by Maharani et al in 2021, on evaluating the suitability of definitive antibiotics in hospitalized patients with Extended-Spectrum Beta-lactamase (ESBL) bacterial infections with the conclusion that 78.6% of definitive antibiotics used met the suitability of type, dose, frequency, and duration (Maharani et al., 2021). Meanwhile, 27.3% of definitive antibiotics that meet suitability have predicted Css_{min} values ≥ MIC and the rest have predicted Css_{min} values < MIC. In general, research related to the evaluation of the suitability of definitive antibiotics in patients with carbapenem-resistant bacterial infections has not been widely done. Therefore, this study wanted to evaluate the suitability of definitive antibiotics used in infection therapy due to carbapenem-resistant bacteria. Furthermore, the calculation of the predicted value of pharmacokinetic parameters on definitive antibiotics that meet the suitability and associated with clinical outcomes to determine the relationship between the value of the minimum level in steady state of the definitive antibiotic given and the clinical outcomes of patients.

2. Research Method

Study design

This study employed a retrospective, descriptive-analytic design. This study evaluated the dosage regimen of definitive antibiotics which used to treat any infection caused by carbapenem resistant bacterial. The appropriate dosage regimen was used to calculate the prediction of antibiotic concentration using pharmacokinetics formula.

Population and samples

The population of this study were patients with carbapenem-resistant bacterial infections who were treated at Dr. Sardjito Hospital Yogyakarta. The inclusion criteria of the study subjects were patients with carbapenem-resistant *P. aeruginosa*, *A. baumannii* or Enterobacterales (*K. pneumoniae* and *E. coli*) bacterial infections who underwent hospitalization ≤45 days, patients received sensitive antibiotic therapy based on the results of culture and sensitivity tests with a duration of administration ≥72 hours, and patients with complete medical record data, while the exclusion criteria of this study was patients with carbapenem-resistant bacterial infections who could not be followed for treatment history and progress.

Study Instruments

The materials in this study were antibiotic sensitivity test data obtained from the Microbiology laboratory for bacterial isolates of *P. aeruginosa*, *A. baumannii*, and Enterobacterales (*K. pneumoniae* and *E. coli*) and medical records of patients with carbapenem-resistant gram-negative bacterial infections who were treated in the January-March 2020 period at Dr. Sardjito Hospital Yogyakarta (Primasari, 2021). The instruments used in this study were data collection sheets and relevant literature. The data collection sheet recorded patient identity, admission and discharge diagnoses, patient progress notes, records of treatment received, patient clinical data, and microbiological examination results, while the relevant literature used, including Clinical Laboratory Standards Institution (CLSI) in 2021, Drug Information Handbook 17th Edition, Antibiotics Guideline, and so on were used to evaluate the suitability of the type, dose, duration, and frequency of definitive antibiotic use.

Data collection

Data collection was carried out at the microbiology installation and medical records installation by reading the medical records of all inpatients who experienced infections due to carbapenem-resistant bacteria who received definitive antibiotics in the January-March 2020 period at Dr. Sardjito Hospital Yogyakarta.

Data analysis

Descriptive analysis was performed on the results of the evaluation of the suitability of definitive antibiotics. Bivariate analysis for the relationship between the predicted value of pharmacokinetic parameters of definitive antibiotics that meet suitability with patient clinical outcomes using the Fisher test. In addition, the calculation of the predicted value of pharmacokinetic parameters was calculated by pharmacokinetic calculation using the following formula.

a. On IV bolus administration

$$Css_{max} = \frac{Div}{Vd}\left(\frac{1}{1-e^{-k.\tau}}\right) \quad (1)$$

$$Css_{min} = Css_{max} \cdot e^{-k.\tau} \quad (2)$$

b. On IV administration of intermittent infusion

$$Css_{max} = \frac{Div/t'}{k.\,Vd}\left(1 - e^{-k.t}\left(\frac{1}{1-e^{-k.\tau}}\right)\right. \quad (3)$$

$$Css_{min} = Css_{max} \cdot e^{-k.(\tau-t)} \quad (4)$$

3. Result and Discussion

The study was conducted by collecting culture and antibiotic sensitivity test data from the Microbiology laboratory to determine which patients had infections due to carbapenem-resistant bacteria. The bacteria observed in this study were limited to P. aeruginosa, A. baumannii, and Enterobacterales which were limited to K. pneumoniae and E. coli, because these two bacteria are known to cause the most infections in patients at Dr. Sardjito Hospital Yogyakarta. The data obtained was the basis for reading the medical records which provided an overview of which patients were hospitalized and which were not. A total of 97 patients with carbapenem-resistant bacterial infections who underwent hospitalization were obtained from the initial screening results.

Furthermore, an evaluation of the 97 patients was done and 23 patients who met the criteria were obtained as research subjects. There were 27 definitive antibiotics used in those 23 patients which were then analyzed for their suitability. Analysis of the suitability of definitive antibiotics included suitability for the administration regimen consisting of type, dose, frequency, and duration. The results of the suitability evaluation provided 11 definitive antibiotics that met the suitability of 11 patients which then were analyzed.

Research subject characteristics

The 11 subjects in this study had various characteristics. The patient characteristics observed in this study were age, gender, treatment room, presence or absence of comorbidities, length of hospitalization, and type of carbapenem-resistant infecting bacteria. The characteristics of the 11 patients can be seen in Table I.

In this study, age characteristics were divided into three groups, namely age less than 18 years, 18-65 years, and more than 65 years. The most patients were from the age group of 18-65 years as many as 5 patients (45.5%). The two extreme age groups (pediatrics and geriatrics) are high-risk or vulnerable age groups exposed to bacterial infections. In the pediatrics group, infections are easy to occur because the immune system has not established well yet, making this group at high risk of infection (Simon et al., 2015). In the geriatric group, infections easily occur due to the decreased function of the immune system. Additionally, the presence of other comorbidities suffered makes the elderly group at high risk of infection. This is in line with Weyand & Goronzy in 2016 who stated that the aging of the immune system is associated with a decrease in the protective ability of the immune system and an increase in the incidence of inflammatory diseases (Weyand and Goronzy, 2016).

The number of female patients was greater than the number of male patients (63.6%). Meanwhile, in another study it was known that 82 patients infected by carbapenem-resistant bacteria, 72% were male (Lin et al., 2016). Balkhair et al. in 2023 also found that of 160 patients with carbapenem-resistant bacterial infections found in blood samples, 71.9% were male. Regarding the patient's treatment room, the number of study subjects who underwent treatment in the ICU room was more than those who underwent treatment in the non-ICU room (Balkhair et al., 2023). A total of 6 out of 11 (54.6%) patients in this study received treatment in the ICU room. This is in line with a study showing that bacterial samples obtained from the ICU room have a higher level of resistance to antibiotics (Morrow, 2013). The incidence of infection due to carbapenem-resistant bacteria is relatively increased in patients admitted to the ICU (Aleidan et al., 2021).

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Table I. Characteristics of patients with definitive antibiotics that meet appropriateness (Primasari, 2021)

Characteristics	Total (n=11)	Percentage (%)
Age (years)		
<18	2	18,2
18-65	5	45,5
>65	4	36,3
Gender		
Male	4	36,4
Female	7	63,6
Treatment room		
ICU	6	54,6
Non-ICU	5	45,4
Comorbidities		
With comorbidities	10	90,9
Without comorbidities	1	9,1
Length of stay		
<7 days	0	0
≥7 days	11	100
Infecting bacteria		
P. aeruginosa	4	36,4
A. baumannii	5	45,4
Enterobacterales		
K. pneumoniae	2	18,2
E. coli	0	0

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A total of 10 (90.9%) patients were known to have comorbidities. The presence or absence of comorbidities can influence the speed of infection cure and length of stay at hospital. The weakened condition of patients with comorbidities makes infection by bacteria that are resistant to various antibiotics easier to occur. In patients with advanced age, an increase in comorbidities is known to proportionally decrease the immune response, where the decreased immune response results in a longer healing time. Regarding length of hospitalization, all study subjects underwent hospitalization for more than seven days. The length of time in the hospital is one of the risk factors for patients to be exposed to carbapenem-resistant bacteria. In addition, the presence of bacterial infection itself is known to affect the length of treatment time and costs that must be incurred. This is in line with the research of Nelson et al. in 2022 which found that patients with carbapenem-resistant Acinetobacter baumannii bacterial infections in America had a long hospitalization time (Nelson et al., 2022). The median length of stay for patients with carbapenem-resistant bacterial infections was found to be 23.5 days (Priyendu et al., 2014). The types of carbapenem-resistant bacteria found in 11 patients, 5 of which were A. baumannii, 4 patients were P. aeruginosa, and 2 were Enterobacterales (K. pneumoniae). Most of the patients were admitted to the hospital in poor condition with various diseases. The presence of several conditions or factors, such as decreased immune system function, advanced age, treatment in the intensive care unit, use of invasive devices, previous antibiotic exposure, organ transplantation, and long hospitalization time are risk factors for carbapenem-resistant bacterial infections (Codjoe and Donkor, 2017; Palacios-Baena et al., 2021).

Evaluation of definitive antibiotics use

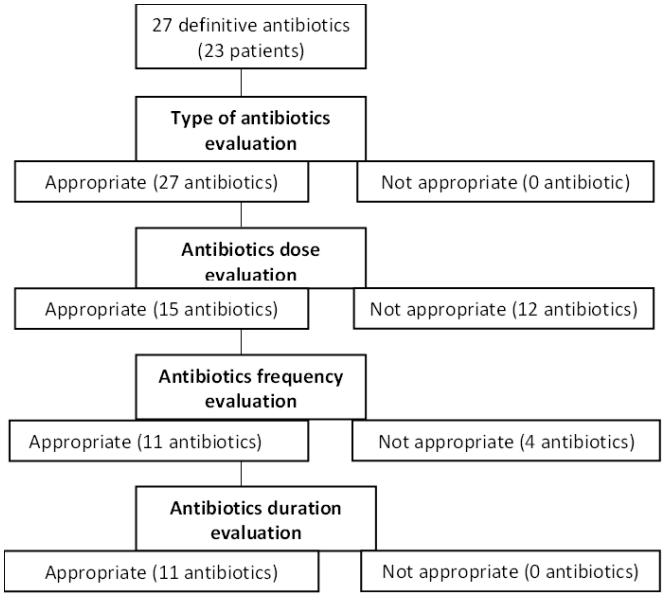

Figure 1. Flow of definitive antibiotic evaluation

Evaluation of antibiotic suitability was carried out by evaluating the type, dose, frequency, and duration of administration based on several guideline or literature, such as Drug Information Handbook, Drug Doses, Neofax 2020, Antibiotics Guideline, IDSA (The Infectious Disease Society of America) Guideline, and other related literature. Appropriateness evaluation was conducted on 27 types of definitive antibiotics used by 23 research subjects. The evaluation began by looking at the suitability of the type based on the type of definitive antibiotic used whether it can be used for therapy in accordance with the diagnosis and looking at the results of culture and sensitivity tests whether sensitive or resistant. Next, the dose of administration was evaluated by comparing the dose given to the patient against the dose in the literature. The following step was doing evaluation of the frequency and followed by the duration of use. The flow of evaluation of the suitability of definitive antibiotics can be seen in Figure 1. Based on the evaluation results, 12 antibiotics were found to be administered at inappropriate (excessive or insufficient) doses. For instance, in the case of dose inaccuracy, one patient diagnosed with a retropharyngeal abscess received amikacin at 500 mg per 24 hours, which was considered too low. According to dosing calculations, the appropriate dose should be 250–375 mg every 8 hours, or a total of 750–1000 mg per 24 hours. In addition, there were 4 antibiotics which given at frequencies that did not align with the literature referenced in the study. As an example, a patient diagnosed with sepsis received cotrimoxazole 960 mg intravenously once daily, whereas the recommended dosing frequency based on the literature is every 12 hours. Finally, as the result of the eavaluation, there were 11 definitive antibiotics that met the criteria for calculation of predicted concentration in body.

Predicted pharmacokinetic parameter values

The pharmacokinetic parameter calculated in this study is the prediction of drug levels in the blood that can be used to determine whether the dose given provides levels below, above or within the therapeutic range. The calculation of the predicted value of definitive antibiotic levels in steady state is calculated by first knowing the pharmacokinetic profile of each antibiotic. Primary parameters such as volume of distribution and clearance, and secondary parameters such as t ½ elimination and elimination constant (k) are based on general population data and obtained from various literature sources.

In this section, the Css_{max} and Css_{min} values were calculated, then the magnitude of the Css_{min} values obtained were compared with the MIC (Minimum Inhibitory Concentration) value. The MIC values were obtained from the AST (Antimicrobial Susceptibility Testing) and CLSI (Clinical and Laboratory Standard Institute) literature in 2021. If the antibiotic level is above or equal to the MIC value, the microorganism can be killed or inhibited by the antibiotic. If the antibiotic level is below the MIC value, the antibiotic cannot kill or inhibit the growth of microorganisms (Hakim, 2014).

The results of the calculation of the Css_{min} value can be seen in Table II. There was 1 definitive antibiotic with a Css_{min} value which reached the MIC value, and 10 other definitive antibiotics had a Css_{min} value less or below the MIC value. The calculation in this study used published pharmacokinetic parameters data of general population from the previous study, which actually pharmacokinetic parameters in one person can be different with the others. Consequently, the exact number of actual antibiotic levels in everyone could not be obtained. As an example, in adult patient who received amikacin during treatment, the volume of distribution value from the literature used is 0.25 L/kg, which can actually different due to the patient's condition. In critical illness, the value of volume of distribution may increase or decrease. Previous study stated several factor that may alter the pharmacokinetic parameters, for instance in critical illness, hypovolaemia and hypoperfusion may reduce the volume of distribution, while fluid shifts and volume resuscitation may increase the volume of distribution (Morales Castro et al., 2023). Amikacin as a member of aminoglycoside antibiotic is a hydrophilic compound which volume of distribution can increase as an impact of pathophysiological changes in critical illness (Roger, 2024). In addition, there was also no MIC data from the Microbiology laboratory from the results of culture and sensitivity tests. So, these results can cause inaccuracy in the results of the comparison between the Css_{min} value and the MIC. The existence of variations between patients, such as the type and severity of the disease, pharmacogenomics or polymorphisms and the presence of other therapies received significantly affect the drug levels in the blood (Hakim, 2014). 1 definitive antibiotic with Css_{min} values reaching MIC values provide worsening outcomes. This can occur because there are many factors that affect the clinical outcome of a therapy, one of which is the patient himself. The patient known to receive the definitive antibiotic ciprofloxacin was a neonate with sepsis due to carbapenem-resistant *K. pneumoniae* bacteria whose disease prognosis was not good since the beginning of treatment.

Relationship between predicted values of definitive antibiotic pharmacokinetic parameters and clinical outcomes

The results of the calculation of Css_{min} values compared to MIC and clinical outcomes can be seen in Table III. 1 definitive antibiotic had a Css_{min} value ≥ MIC with clinical outcomes not improved. In contrast, the calculation results of 10 other definitive antibiotics showed Css_{min} values < MIC with clinical outcomes improved by 60% and not improved by 40%. Ideally, to measure the drug concentration which may beneficial for dose optimization, safety and efficacy assessment of antibiotics, therapeutic drug monitoring (TDM) implementation is needed to be done. In this study, there are several patients who got aminoglycoside, such as amikacin and gentamicin where actually, TDM is recommended to be done due to its narrow therapeutic index. Although traditionally used for medications with a narrow therapeutic index, the use of TDM is becoming more widespread. This is driven by the growing number of patients with poorly characterized pharmacokinetics, such as the critically ill, those with multiple comorbidities, the elderly, and individuals at the extremes of body size, as well as the emergence of less susceptible pathogens that may necessitate higher antimicrobial doses to achieve optimal therapeutic outcomes (Roberts et al., 2012; Williams et al., 2024). Since most of population of this study in critical stage with multiple comorbidities, TDM is also highly recommended to be implemented.

Table 2. The results of the calculation of the predicted values of pharmacokinetic parameters and their comparison against the MIC value (Primasari, 2021)

Patient code	Antibiotic regimen	Css_{min} (mcg/ml)	Pathogenic bacteria	MIC (mcg/ml)	Description	Clinical outcome
P1	Amikacin 1500mg/24 hours	0,06	*P. aeruginosa*	≤16	Below MIC value	NI
P2	Cefepime 2000mg/12 hours	2,48	*P. aeruginosa*	≤8	Below MIC value	NI
P4	Tigecycline 8mg/12 hours	0,09	*A. baumannii*	≤2	Below MIC value	I
P6	Cotrimoxazole 960mg/12 hours		*A. baumannii*	≤10	Below MIC value	I
	Trimethoprim 160mg	2,45				
	Sulfamethoxazole 800mg	28,59				
P8	Gentamicin 80mg/8 hours	0,19	*K. pneumoniae*	≤4	Below MIC value	I
P9	Amikacin 175mg/8 hours	1,91	*P. aeruginosa*	≤16	Below MIC value	I
P10	Amikacin 1000mg/48 hours	$2,63 \times 10^{-5}$	*A. baumannii*	≤16	Below MIC value	NI
P11	Cotrimoxazole 960mg/12 hours		*A. baumannii*	≤10	Below MIC value	I
	Trimethoprim 160mg	3,24				
	Sulfamethoxazole 800mg	38,08				
P12	Amikacin 1000mg/24 hours	0,05	*A. baumannii*	≤16	Below MIC value	NI
P17	Amikacin 1000mg/24 hours	0,04	*P. aeruginosa*	≤16	Below MIC value	I
P22	Ciprofloxacin 15mg/12 hours	3,17	*K. pneumoniae*	≤0,25	Above MIC value	NI

Notes: I = Improved, NI = Not Improved

Table III. Predictive value of Css_{min} compared to MIC and clinical outcomes (Primasari, 2021)

Predicted drug concentration	Clinical outcome				Total n (%)
	Improved		Not Improved		
	n	%	n	%	
Appropriate (above MIC value)	0	0	1	100	1 (9,1)
Not appropriate (below MIC value)	6	60	4	40	10 (90,9)

Howerer, considering this is a retrospective study and TDM has not been implemented well in Indonesia, the phenomenon shown in Table III can occur because the antibiotic concentrations were not obtained from measurement using blood samples from several time points. All concentrations were got from the calculation using pharmacokinetic parameters in the general population available from previous publications to be inputted in the pharmacokinetic formula which has been explained at the method section. Therefore, the predicted concentration might be different with the actual. As the result, the actual value of C_{ssmin} can be higher or less than this study finding. Additionally, the value of MIC in this study was also not the exact MIC which obtained from laboratory test results due to limitation of data access, so the actual MIC value could be less than the standard used in this study. These conditions may cause different interpretation in evaluating C_{ssmin} attainment to MIC value.

Analysis of the relationship between predicted values of definitive antibiotic pharmacokinetic parameters and clinical outcomes in this study was performed using the Fisher test. The test was conducted using 95% confidence level and α of 0.05. The test results showed a p value of 0.455 with the conclusion that there was no relationship between the predicted value of definitive antibiotic pharmacokinetic parameters that met the suitability with the clinical outcomes of patients in this study. However, the small number of samples in this study makes the conclusions obtained cannot be generalized.

Theoritically, concentration antibiotic attainment to the range therapeutic may increase the successful in eradicating pathogen bacteria and give improvement to patients. From this study finding, there was one patient with C_{ssmin} value met the MIC, but no improvement observed. There are many aspects that can cause treatment failure. Since the beginning of treatment, the prognosis of the disease was not good. Patient was neonates who was born with low birth weight and had pneumonia from the beginning of the treatment. Studies stated that in general, neonates do not have a mature defense system which makes this group is at high risk of infection (Basha et al., 2014; Tsafaras et al., 2020). The patient was diagnosed with late-onset sepsis caused by carbapenem-resistant *K. pneumoniae* bacteria resistant to carbapenem after several days of treatment in the hospital. Based on the antibiotic sensitivity, ciprofloxacin 15 mg twice daily was given to the patient. The treatment in this case was quite challenging, especially since low birth weight put the baby at high risk of death (Coggins and Glaser, 2022). Although predicted ciprofloxacin concentration reached the MIC, there was no improvement and resulting in death of patient. Meanwhile, there were 6 patients with C_{ssmin} couldn't meet the MIC value and improved may cause by the effect from previous empirical antibiotic. Besides that, the penetration ability of each antibiotic to the site of infection also has responsibility in giving effect to the patient. Even though the amount in serum is small, the concentration that reaches the site of infection is capable and effective in eradicating the infecting bacteria.

Most of patients in this study were treated at intensive care unit which were in critical condition. Managing infections in critically ill patients presents distinct challenges for healthcare professionals (Roger, 2024). Critical illness induces various pathophysiological changes that can significantly impact drug exposure. Haemodynamic, metabolic, and biochemical disturbances in these patients may alter pharmacokinetic and pharmacodynamic parameters, making dose optimization particularly complex. These conditions can affect protein binding, volume of distribution, ionization, oral absorption, hepatic and intestinal metabolism, as well as renal clearance (Morales Castro et al., 2023). Changes in pharmacokinetic parameters may result in different doses required to reach the therapeutic target concentration compared to other conditions. Therefore, to be able to ensure that the expected antibiotic concentration can be achieved, it is necessary to monitor antibiotic blood levels after administration, which the results of the examination can be used as a reference in determining the patient's pharmacokinetic parameters which beneficial for calculating the amount of individual dose needed.

Research limitations and recommendation

The Enterobacterales bacterial groups observed in this study were limited to *K. pneumoniae* and *E. coli*. The study was only conducted retrospectively, so the exact condition and clinical outcomes of the patients could not be known. Time limitation was also an obstacle, so the number of samples obtained did not represent the general population enough to be statistically analyzed. The limited number of samples also meant that multivariate analysis could not be conducted to determine how much influence several confounding variables had on the dependent variable, in this case the patient's clinical outcome. In addition, the supporting data needed to calculate the prediction of pharmacokinetic parameter values in this study is based on literature according to the population in general, so it cannot be known precisely for each individual patient involved in the study. Therefore, further studies that measure the plasma concentration of antibiotics with a larger number of samples and the use of PK/PD parameters in assessing the effectiveness of antibiotics need to be carried out.

4. Conclusion

The results of the suitability of definitive antibiotics in patients with carbapenem-resistant bacterial infections at Dr. Sardjito Yogyakarta General Hospital were 11 (40.7%) antibiotics that met the suitability of type, dose, frequency, and duration of the 27 definitive antibiotics analyzed. Prediction of pharmacokinetic parameter values of 11 definitive antibiotics in patients with carbapenem-resistant bacterial infections in the form of minimal levels in the blood at steady state compared to the MIC value, 1 definitive antibiotic (9.1%) has a Cssmin value > MIC and 10 other definitive antibiotics (90.9%) have a Cssmin value < MIC. In addition, there is no relationship between the predicted value of definitive antibiotic pharmacokinetic parameters that meet regimen suitability and clinical outcomes in patients with carbapenem-resistant bacterial infections at Dr. Sardjito Hospital Yogyakarta.

Acknowledgment

The authors would like to thank the antimicrobial stewardship (PPRA) team, clinical microbiology laboratory, and medical records installation of Dr. Sardjito Hospital Yogyakarta for providing the data needed for this study.

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