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Research Paper

Amikacin Dosing Analysis in Sepsis Treatment: A Pharmacokinetic Study Based on Therapeutic Drug Monitoring

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ABSTRACT:
Objectives: *The primary purpose of this research was to evaluate the loading dose and maintenance dose of amikacin in the treatment of sepsis from intensive care unit (ICU) patients from May to July 2023 at the dr. Ramelan Naval Central Hospital in Indonesia. The analysis focus on the use of therapeutic drug monitoring (TDM) results to improve efficacy and safety of amikacin therapy.*
Material and Methods: *A total of 8 sepsis patients received amikacin for 5 days. The loading dose was administered regardless of the renal function and was calculated of 7.5mg / kg body weight, administered intravenously as a bolus. The subsequent maintenance dose was delivered 4 hours following the loading dose at 15mg / kg body weight by an intermittent drip for 1 hour. The TDM measurement was conducted twice on the third day, with sampling conducted at 1.5 and 4 hours following the administration of the third amikacin maintenance dose.*
Results: *The TDM results revealed that the amikacin t½ elimination was 4.97 □ 3.65 hours, distribution volume was 20.64 □ 5.12 %, and amikacin clearance occurred at a rate of 39.54 □ 19.59 mL/min. A total of seven patients demonstrated Cpmax/MIC indices exceeding 8, while three patients exhibited AUC0-24h/MIC indices surpassing 75. The data showed variabilities in pharmacokinetic characteristics of amikacin in the sepsis patients due to comorbidities specifically patient's creatinine clearance.*
Conlusion: *The dose administered at efficacious doses attaining the desired PK/PD target while minimizing the risk of toxicity The findings of pharmacokinetic parameters on septis patient in Indonesia give valuable insights into the potential of amikacin therapy to enhance the possibility of achieving an effective treatment.*
KEYWORDS: *Amikacin, Therapeutic Drug Monitoring, Sepsis, Pharmacokinetic, Pharmacodynamic*

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I. INTRODUCTION

Sepsis is a critical condition that is occurred mostly in the intensive care unit (ICU) and the major cause of morbidity and mortality. Amikacin, an aminoglycoside antibiotic, is effective in treating sepsis and often used in combination with β-lactam antibiotics to broaden the spectrum against multi-drug resistant (MDR) pathogens such as Extended-spectrum beta-lactamase (ESBL) group in Enterobacter, and also carbapenem resistant group of gram negative.1,2 The presence of antibiotic-resistant bacteria in health services is a serious problem, so appropriate antibiotic sensitivity is needed for the treatment of infections.3,4 The optimization of amikacin use has become medically urgent due to increasing antibiotic resistance.5,6 Determining appropriate loading and maintenance doses of amikacin is crucial for improving patient survival in the ICU.

Amikacin exhibits low protein binding (<20%) and specific pharmacokinetic properties in septic patients, including elimination half-life 5.4 hours, distribution volume 42%, and total clearance 3.3 mL/min.7,8 The pharmacodynamics effect depend on concentration (concentration dependence), the higher the concentration the better the bacterial killing power.9

However, there is limited data on interethnic differences in the pharmacokinetics of amikacin. Generally, the use of antibiotics in Asian and Caucasian patients showed pharmacokinetic variabilities, due to differences in distribution volume and elimination rate, but no scientific evidence showed differences of amikacin's pharmacokinetic among African, American, Caucasian, Asian, and Hispanic races because of their hydrophilic properties and complete excretion in the kidneys. However, the Alaskan population showed an exception to aminoglycoside use, with slower elimination and a wider distribution volume than the American population.10

Amikacin is known for its nephrotoxic and ototoxic potential, which necessitates careful therapeutic drug monitoring (TDM) to ensure effective therapeutic levels while avoiding toxic effects. Nephrotoxicity causes impaired kidney function, while ototoxicity results in permanent hearing loss, which can occur with aminoglycoside antibiotic therapy.1,5 TDM is essential not only to achieve the desired pharmacokinetic/pharmacodynamic (PK/PD) indices targets but also to minimize the risk of these adverse effects by adjusting doses based on individual patient pharmacokinetics.7,8 Pharmacokinetic data in Indonesia is still very limited, especially for amikacin, which is a drug with a narrow therapeutic window.This approach helps optimize the therapeutic efficacy of amikacin while maintaining patient safety.11,12

Patient with suspected sepsis admitted to ICU will receive therapy of amikacin at the dr. Ramelan Naval Central Hospital in Indonesia based on body weight. Amikacin therapy in hospitalized patients is given intravenously (i.v.) with a loading dose of 7.5 mg/kgBW, then continued 4 hours later by a maintenance dose 15 mg/kgBW (i.v. intermittence in 1 hour) every 24 hours. Loading dose aims to achieve antibiotic levels that exceed the MIC to kill bacteria. The impact of antibiotic therapy is then observed by monitoring clinical outcomes and pharmacokinetic/pharmacodynamic (PK/PD) indices.

This prospective pharmacokinetic approach study will build on previous findings by providing more relevant data for Indonesian sepsis populations, which may show different pharmacokinetic characteristics from previously studied populations.

II. MATERIALS AND METHODS

Clinical pharmacokinetic study should be conducted in accordance with the Helsinki Declaration and Good Clinical Practice (including International Conference on Harmonization [ICH] version).[1] A prospective study was performed on patients admitted to the intensive care units (ICUs) at the dr. Ramelan Naval Central Hospital between May and July 2023. The protocol was approved by the Research Ethics Committee dr. Ramelan Naval Central Hospital (Ethical approval No.: 17/EC/KEP/2023). All patients or their legal represent Patients were eligible for inclusion if (1) they were admitted to the ICU; (2) they suffered from a severe infection caused by a Gram-positive microorganism and were therefore treated with amikacin; (3) patients or their legal representatives were informed about this study and written informed consent was obtained; and (4) it was possible to obtain plasma samples. The exclusion criteria were (1) age <18 years; (2) pregnancy; and (3) hypersensitivity to amikacin. Demographic, clinical, and biochemical data at the time of inclusion in the study were obtained for all patients.

Patients who fulfilled the inclusion criteria received 500 or 750 mg loading dose amikacin and followed by maintenance dose 1.000 to 1.250 mg amikacin every 24 hours by intermittence i.v. infusion over 1 hour. Blood samples were collected on steady state conditions (at day 3rd) after the third maintenance dose, samples were taken at 1.5 and 4 hours respectively. Whole blood sample collected with BD Vacutainer K3E 3 mL by a nurse. Collected plasma samples were centrifuged and the plasma was stored at -18°C until analysis. The following parameters were obtained: CrCL estimated by the Cockroft-Gault formula, distribution volume (Vd), elimination half-life ($t_{½}$), area under the curve (AUC) and total clearance (CL).

Amikacin plasma concentrations were quantified using a previously developed and validated Ultra-Performance Liquid Chromatography–Tandem Mass Spectrometry (UPLC-MS/MS) bioanalytical method.[2] This quantification is simple and faster than the new method that also developed in Indonesia recently.[3] The bioanalytical procedure of amikacin involved a UPLC BEH C18 column as a stationary phase, with an employed mobile phase consisting of 0.1% v/v formic acid and acetonitrile (85:15 v/v). The flow rate was set at 0.1 ml/min, and the column temperature was kept at 30°C. Kanamycin was selected as an internal standard. Amikacin and kanamycin were determined at a mass-to-charge ratios (m/z) of 585.9>162.9 and 484.67>162.83, respectively. The amikacin bioanalysis method in the plasma matrix at the optimum separation condition was validated and parameters such as selectivity, linearity, accuracy, precision, recovery, carry-over, matrix effect, and sample stability were determined.[4] The optimum conditions of sample preparation were obtained through liquid-liquid extraction using trichloroacetic acid, followed by vortex mixing for one minute and centrifugation at 10,000 rpm for five minutes. Ten µL of supernatant was collected and injected to the system. A linear response was achieved in the 1.0-150.0 µg/ml range with R^2 0.9997. Accuracy and precision met the requirements with % differences and coefficient variation at all concentration levels less than 15% and at the lower limit of quantification (LLOQ) level (1 µg/mL) less than 20%.

Statistical analysis using Principal Component Analysis (PCA) was applied to capture the direction of highly variable patient pharmacokinetic parameters, including gender, age, weight, BMI, loading dose, maintenance dose, creatinine clearance (CrCL), serum albumin, elimination half-life ($t_{½}$), amikacin clearance(CL Amikacin), $C_p$max/MIC indices, $AUC_{0\text{-}24h}$/MIC indices, and steady-state minimum concentration (C_{ss}min).

III. RESULT

Among the 14 patients in the ICU at the dr. Ramelan Naval Central Hospital in Indonesia were using amikacin during the observation period of this study, 8 patients met the inclusion criteria. These 8 subjects were treated with amikacin protocol involved a loading dose of 7.5 mg/kgBW, followed 4 hours latter by a maintenance dose of 15 mg/kgBW administered via intermittent intravenous infusion over 1 hour every 24 hours. Serum amikacin concentrations were measured at specified times after 3rd maintenance dose and analyzed using UPLC-MS/MS.

The demographics and clinical characteristics of the patients participating in this study are presented in Table 1. This population pharmacokinetic study included subjects ranging from 62 to 80 years old, majority being elderly patients (>65 years old) only 2 patients were adults (<65 years old). The mean of creatinine clearance (CrCL) was 42.5 mL/min in the range of 15.7 - 115 mL/min, indicating a reduction in glomerular filtration rate (GFR) in most patients, with only one patient exhibiting stage 1 kidney disease.

Table 1. Clinical characteristics and data distribution of ICU patients using amikacin

Parameter	Mean ± SD	Range
Gender (Male / Female)	6/2	-
Age (years)	71.3 ± 7.3	62 - 80
Weight (kg)	59.8 ± 11.3	48 - 80
BMI (kg/m^2)	21.2 ± 3.4	17.3 - 27.7
Serum creatinine (mg/dL)	2 ± 1.2	0.5 - 3
CrCL* (mL/min)	42.5 ± 35.0	15.7 - 115

BMI, Body Mass Index; SD, standard deviation; CrCL, creatinine clearance; *calculated according to the Cockcroft-Gault equation.

Five patients had BMI values between 18.5 and 24.9 kg/m² which is considered normal according to the World Health Organization (WHO). Two patients were underweight, and one patient was overweight. Even though there were differences in patient weight, the majority were grouped as normal BMI, so it was not a factor that was analyzed further in this study.

All patients suffered from sepsis and other comorbidities. Pneumonia dominated as a major comorbid (n=5), followed by encephalopathy with multiple organ dysfunction syndrome (n=2), and lung tuberculosis (n=2), the complete patient's comorbidities can be seen on table 2. The individual loading dose and maintenance dose of amikacin on patient, serum creatinine, serum albumin, and stage kidney disease each patient also presented on table 2.

Table 2. Comorbidities and supporting laboratory data of ICU patients using amikacin

Patient Code	Comorbids	LD/MD (mg)	Serum Cr (mg/dL)	Serum Albumin (mg/dL)	Stage Kidney Disease
P1	Pneumonia; Acute respiratory distress syndrome (ARDS); Bilateral inguinal hernia	500 / 1000	0.5	2.49	1
P2	Pneumonia; Cerebral infarction	500 / 1250	1.9	3.35	3
P3	Encephalopathy; Multiple organ dysfunction syndrome (MODS); Cerebrovascular accident (CVA) Infark	500 / 1000	2.7	2.72	4
P4	Pneumonia; Gastroenteritis; Spondylitis	500 / 1000	1.9	2.88	4
P5	Pneumonia; Pleural effusion; Cardiomegaly	750 / 1250	4.0	3.00	4
P6	Tuberculosis; Thyroid nodules	500 / 1000	0.7	2.57	2
P7	Pneumonia; Left lobe atelectasis; Suspected laryngeal cancer	500 / 1000	1.1	1.54	3

P8	Tuberculosis; Encephalopathy; MODS	500 / 1000	3.0	0.03	4

LD, loading dose; MD, maintenance dose; Cr, creatinine

Loading doses and maintenance doses are basically calculated based on weight, and in practice are rounded for ease of preparation. Loading dose approaching to 500 or 750 mg amikacin given with bolus administration and maintenance dose approaching to 1000 or 1250 mg amikacin given by intermittent infusion for one hour, with adjusting from the clinician to the severity conditions of patient. Stages kidney disease among the patients were as follows: stage 1 (n=1), stage 2 (n=1), stage 3 (n=2), and stage 4 (n=4).

Individual pharmacokinetic parameters of amikacin calculated from TDM data at 1.5 and 4 hours after the start of administration of the third maintenance dose of amikacin can be seen in table 3. The parameters were obtained from the first-order kinetics of drug elimination to calculate the elimination rate constant (Ke) from two therapeutic drug monitoring (TDM) data points that collected, elimination half-life ($t_{½}$), distribution volume (V_d), and amikacin clearance (CL) using equations (1), (2), (3), and (4) respectively.

$$K_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} \quad (1)$$

Where:
$C_1$is the plasma drug concentration at the first time point (t_1)
C_2 is the plasma drug concentration at the second time point (t_2)
t_1 and t_2 are the times at which the C_1 and C_2 were measured, respectively

$$t_{½} = \frac{\ln 2}{K_e} \quad (2)$$

Where:
ln(2) is the natural logarithm of 2, approximately 0.693
K_e is the elimination rate constant

$$V_d = \frac{Dose}{C_0} \quad (3)$$

Where:
Dose is the amount of drug administered
C_0 is the initial plasma drug concentration (extrapolated concentration at time zero)

$$CL = K_e \times V_d \quad (4)$$

Table 3. Pharmacokinetic parameters of Amikacin in the ICU patients

Patient Code	K_e (/hours)	$t_{½}$ (hours)	Vd (%)	CL Amikacin (mL/min)
P1	0.24	2.93	20.14	47.69
P2	0.30	2.29	18.24	59.88
P3	0.11	6.33	25.60	23.35
P4	0.07	9.29	18.09	10.79
P5	0.39	1.78	12.85	66.59
P6	0.23	3.00	21.61	41.67
P7	0.26	2.65	18.94	45.39
P8	0.06	11.46	29.67	20.93
	0.21 ± 0.12	4.97 ± 3.65	20.64 ± 5.12	39.54 ± 19.59

The pharmacokinetic parameters of amikacin in Indonesian sepsis patients were compared with data from various populations, revealing significant differences in drug clearance (CL) and elimination half-life ($t_{½}$). The $t_{½}$ values for patients with stage 1, 2, and 3 kidney disease are relatively similar to population data, while stage 4 kidney disease patients show very different values.

The pharmacokinetic/pharmacodynamic (PK/PD) indices are crucial for understanding the efficacy and safety of amikacin therapy in ICU patients. These indices include the ratio of peak plasma drug concentration to minimal inhibitory concentration ($C_p$max/MIC), the ratio of the area under the curve over 24 hours to MIC

($AUC_{0\text{-}24h}$/MIC), and the predicted steady-state minimum plasma drug concentration (C_{ss}min) were presented on table 4.

C_{ss}min is the predicted minimum concentration of amikacin at the steady state, which is critical to avoid toxicity, particularly nephrotoxicity. It is recommended that C_{ss}min should not exceed Minimum Toxic Concentration (MTC)-Trough (10 µg/mL).[5] In the literature, C_{ss}min is usually calculated by using equation (5) to describe the plasma profile without a loading dose, resulting in a lower value than the actual concentration. In this study, the C_{ss}min value produced is closer to the actual number because it takes into account the loading dose given, as seen in equation (6) and the simulated plasma concentration-time curve can be seen more clearly in Figure 1.

$$C_{ss}min = \frac{Dose}{V_d} \times e^{-K_e \tau} \quad (5)$$

Where:
Dose is the amount of drug administered
τ is interval of administration

$$3rd\ C_p p\ Trough = \frac{LD}{V_d} \times e^{-K_e 76} + \frac{MD}{V_d} \times e^{-K_e 71.5} + \frac{MD}{V_d} \times e^{-K_e 43.5} + \frac{MD}{V_d} \times e^{-K_e 23.5} \quad (6)$$

Table 4. Pharmacokinetic/Pharmacodynamic Indices and C_{ss}min of ICU patients using amikacin

Patient Code	$C_p$max/MIC Indices	AUC $_{0\text{-}24h}$ /MIC Indices	C_{ss}min (µg/mL)*
P1	10.3	43.6	0.32
P2	13.2	43.5	0.09
P3	9.8	82.8	6.44
P4	14.4	160.8	24.05
P5	15.2	39.2	0.01
P6	11.6	49.9	0.40
P7	12.0	45.9	0.21
P8	6.0	76.2	15.23

* The 3rd Cp trough value based on pharmacokinetic model calculated at t = 76 hours

$C_p$max/MIC indices is a measure of the peak plasma drug concentration relative to the MIC (8 µg/mL) of the pathogen.[6] A ratio of at least 8 is generally considered necessary for optimal antibacterial activity.[7]·[8] $AUC_{0\text{-}24h}$/MIC indices represents the total drug exposure over 24 hours relative to the MIC, with higher values indicating better efficacy if more than 75 ratio.[9]

The PK/PD indices of amikacin in these ICU patients show significant variability. The $C_p$max/MIC indices ranged from 6.0 to 15.2, while the $AUC_{0\text{-}24h}$/MIC indices varied from 39.2 to 160.8. These indices are crucial for determining the efficacy of amikacin, as the $C_p$max/MIC indices of at least 8 is generally considered necessary for optimal antibacterial activity. In this study, most patients achieved this target, indicating effective peak concentrations relative to the MIC. Fewer patients achieved the target AUC0-24 hour/MIC indices, only three patients had more than 75.

The predicted steady-state minimum concentrations (C_{ss}min) also varied widely, from 0.01 to 24.05 µg/ml. These values are important for assessing the risk of toxicity, in particular nephrotoxicity, which is an adverse effect of aminoglycosides such as amikacin. In this study, patients 4, and 8 had C_{ss}min values significantly higher than 10 µg/mL, indicating a high risk of nephrotoxicity. Specifically, patient 4 had the highest Cssmin value of 24.05 µg/ml, which is well above the safe threshold and suggests a substantial risk of nephrotoxicity. The best target was achieved by patient 3 who met the PK/PD indices target and also the safety of C_{ss}min.

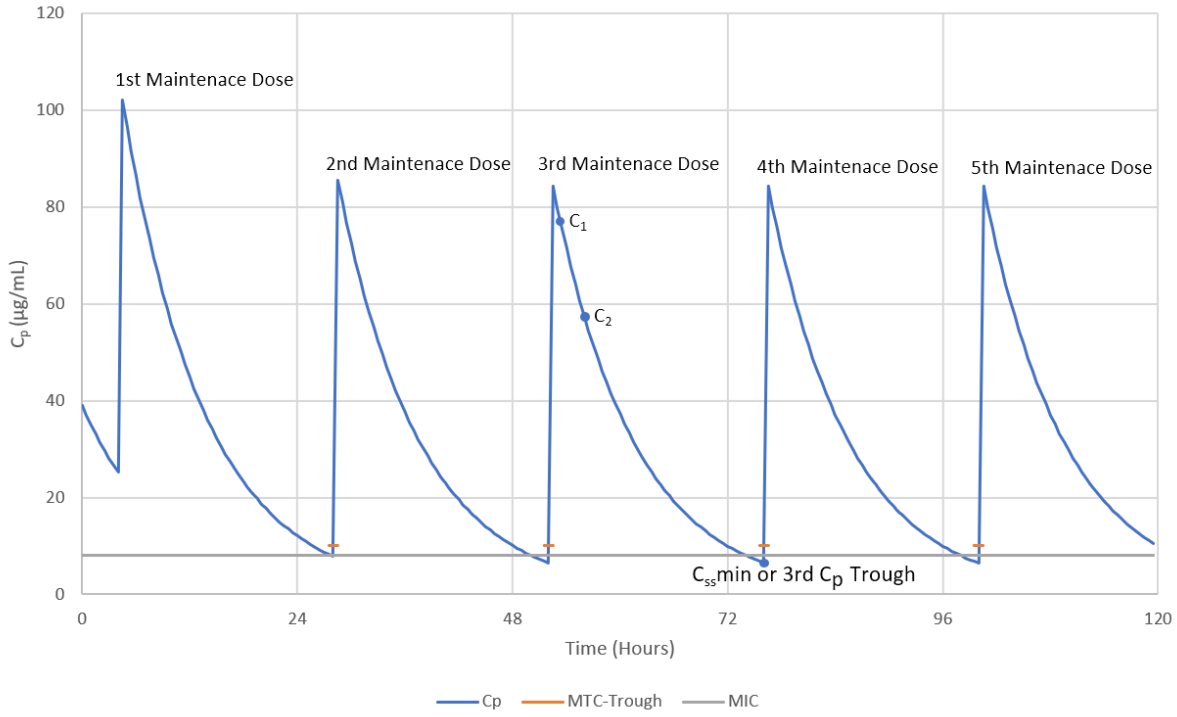

Figure 1. Plasma concentration-time curve simulation base on Patient 3 individual pharmacokinetic value

Given the complexity of pharmacokinetic data in this study, we employed multivariate statistical analysis to understand the relationships between multiple variables simultaneously. This analysis is particularly useful in clinical pharmacokinetics to assess drug efficacy and safety across different patient demographics and physiological conditions.[1] The dataset provided includes various pharmacokinetic parameters for eight patients (P1 to P8), including gender, age, weight, BMI, loading dose, maintenance dose, creatinine clearance (CrCL), serum albumin, elimination half-life ($t_{½}$), clearance of amikacin (CL Amikacin), $C_p$max/MIC indices, $AUC_{0\text{-}24h}$/MIC indices, and steady-state minimum concentration (C_{ss}min).

Principal Component Analysis (PCA) is a simple, nonparametric method for extracting relevant information from datasets, identifying patterns in data, and expressing differences. PCA is applied for the reduction of dimensionality and multivariate data compression exploration within different fields of science.[10],[11] The score plot of 8 patients distribution across principal components can be seen in Figure 2 and the PCA loading plot of pharmacokinetic parameters can be seen in Figure 3.

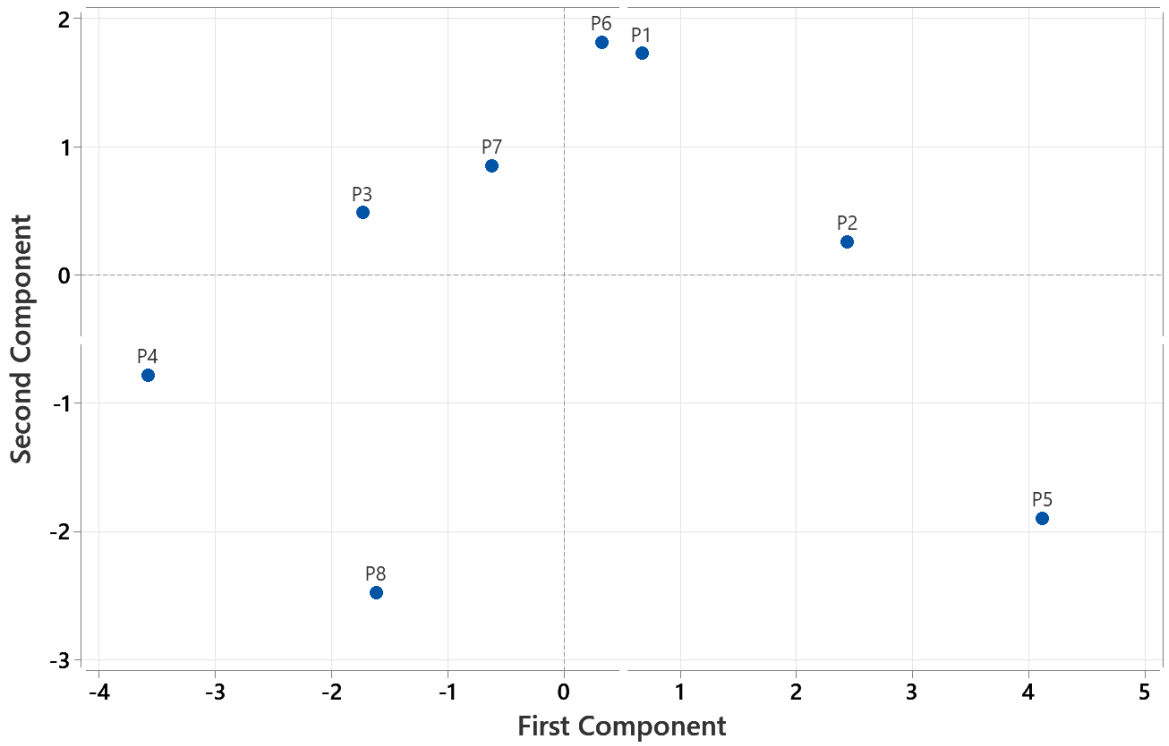

Figure 2. PCA Score Plot of Patient Distribution Across Principal Components

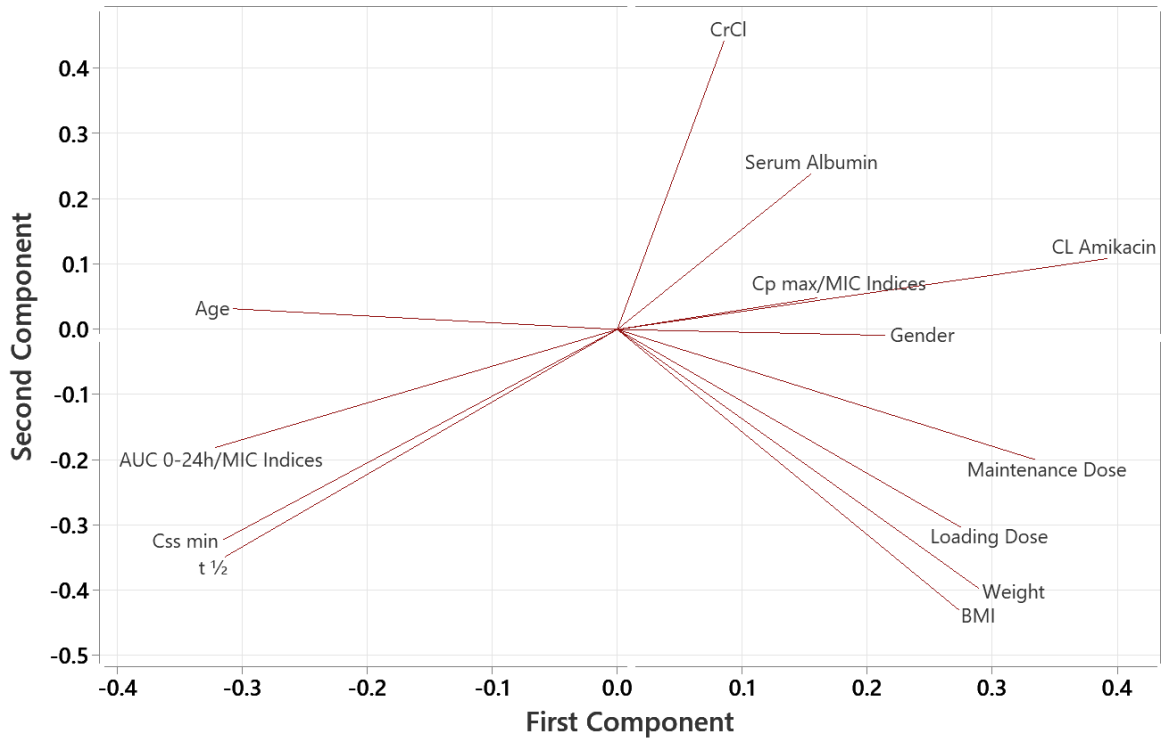

Figure 3. PCA Loading Plot of Pharmacokinetic Parameters

The PCA reveals three distinct groups of patients based on their pharmacokinetic profiles. Figure 2 show the majority of the patients (P1, P3, P4, P6, P7, P8) have mean negative values for First Principal Component (PC1) and mean positive value for Second Principal Component (PC2), indicating their relatively similar pharmacokinetic profiles that differentiate them from the two other patients. P2 with positive values for both PC1 and PC2, indicating another distinct profile. P5 stands out due to the highest positive value for PC1,

but negative value for PC2, this is demonstrated by distinct pharmacokinetic profile with a lower elimination half-life (t ½) and higher clearance (CL Amikacin).

PC1 variables such as CrCL, Serum Albumin, BMI, and Weight significantly influence the components and, therefore, play an essential role in differentiating patient profiles based on their pharmacokinetics. Amikacin elimination half-life ($t_{½}$) and C_{ss}min variables have strong negative loadings on PC2, indicating they contribute significantly but in the opposite direction compared to CrCL and Serum Albumin. Age and gender variables have a relatively small influence on both PC1 and PC2.

IV. DISCUSSION

Creating a Function M-File Using the above information, the following m.file can be created in MATLAB in which:

Demographic data suggest that a large proportion of elderly patients have impaired renal function, and these data are important because amikacin is primarily eliminated in the urine.[12] Four patients with severe renal impairment exhibited anomalies, particularly patient 5, who had longest $t_{½}$ values and the highest BMI among the eight patients. Patient 8 had the smallest $t_{½}$ values, which correlated with the lowest serum albumin level. These variations are likely due to the renal elimination of amikacin, as renal function significantly impacts drug clearance and distribution [13].

A study on the population pharmacokinetics of amikacin in a Korean clinical population reported a clearance rate of 47 mL/min and a elimination half-life of 3.5 hours, with a distribution volume of 18.2%.[14] These values indicate a faster drug elimination in Koreans compared to the Indonesian ICU patients, who had an average clearance rate of 39.54 mL/min and elimination half-life of 4.97 hours. Further comparisons across different ethnicities, including Asian, Hispanic, North African, and Caucasian populations, showed that the clearance rates and half-lives were generally higher and shorter, respectively, than those observed in the Indonesian ICU patients. Specifically, the clearance rates for these populations ranged from 50 to 58.3 mL/min, with half-lives between 3.6 and 4.0 hours.[15] This suggests a slower elimination process in the Indonesian patients.

In critically ill Kuwaiti patients, the pharmacokinetic parameters were closer to those observed in the Indonesian ICU patients, with a clearance rate of 46.7 mL/min and elimination half-life half-life of 4.5 hours, and a distribution volume of 17.5%.[16] These similarities indicate that critically ill conditions may influence pharmacokinetic behavior in a comparable manner across different populations. Overall, the pharmacokinetic parameters of amikacin in Indonesian ICU patients show some variability compared to other populations. The average clearance rate and elimination half-life in Indonesian patients are generally lower and longer, respectively, compared to other ethnic groups, indicating a slower elimination process. This highlights the importance of individualized dosing and therapeutic drug monitoring (TDM) to optimize therapeutic outcomes and minimize toxicity in different populations. Potential factors influencing these differences include genetic variations, environmental factors, or the severity of critical illness.

The two PK/PD indices of amikacin in this study show variability. Only one patient (patient 8) had a $C_p$max/MIC indices of 6 times even though the $AUC_{0\text{-}24h}$/MIC indices was more than 75 times, indicating that the effectiveness of antibiotic exposure is high enough to eliminate bacteria over a longer period of time. Based on recent research, it has been proven that there is no correlation between the observed PK/PD indices $C_p$max/MIC and $AUC_{0\text{-}24h}$/MIC, so the dissimilarity in the results of these two PK/PD measurements is normal.[17] However, to achieve the $AUC_{0–24h}$/MIC target, a significant increase in dose is required compared to the dose required for Cmax/MIC, especially in patient 8 which C_{ss}min data of more than 10 µg/mL indicates a risk of nephrotoxicity.[5]

The multivariate analysis underscores the importance of considering multiple patient-specific factors in pharmacokinetic studies. For instance, renal function significantly affects drug clearance, as evidenced by the correlation between creatinine clearance and amikacin clearance. This finding aligns with established pharmacokinetic principles that impaired renal function can lead to drug accumulation and potential toxicity.

Hierarchical clustering analysis revealed that Patients P1, P3, P4, P6, P7, and P8 formed a group with similar pharmacokinetic profiles, indicating that they were more similar. Patients P2 and P5 formed 2 other groups, with different characteristics. Multivariate analysis underscored the importance of considering several patient-specific factors in pharmacokinetic studies. For example, renal function significantly affected drug clearance, as evidenced by the correlation between creatinine clearance and amikacin clearance. This finding is in line with the general pharmacokinetic principle that impaired renal function can lead to drug accumulation and potential toxicity..

Research Limitations: The limitation of this study is that the laboratory data for each patient is not the same and incomplete, for example data on leukocyte counts to support the clinical outcomes of amikacin therapy. This is due to the need for patient laboratory tests determined by the doctor and depends on patient's health coverage.

V. CONCLUSION

Amikacin loading dose and maintenance dose were given to sepsis patients in the ICU at RSUD dr. The Ramelan Naval Center Hospital in Indonesia effectively achieved the desired PK/PD target with 7 patients achieving the Cpmax/MIC index target, and 6 patients were at minimal risk of toxicity as indicated by Cssmin values below the MTC-Trough. The diversity of amikacin pharmacokinetic characteristics in sepsis patients is caused by comorbidities, especially the stage of kidney disease. The findings of pharmacokinetic parameters (amikacin elimination t½, amikacin clearance, and distribution volume) in sepsis patients in Indonesia provide valuable insight into the potential of amikacin therapy to increase the chances of achieving effective treatment in this country.

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Ethics

Ethics Committee Approval: Research Ethics Committee dr. Ramelan Naval Central Hospital (Ethical approval No.: 17/EC/KEP/2023)

Informed Consent: All subjects consented to participate in the clinical study (obtained from patients relatives).

Authorship Contributions: Surgical and Medical Practices: T.S., W.W., P.H., Concept: T.S., H.L., H.N., Design: T.S., H.L., W.W., Y.H., P.H., R.R., Data Collection or Processing: T.S., H.L., W.W., H.N., Y.H., R.R., Analysis or Interpretation: T.S., H.L., W.W., H.N., Y.H., P.H., R.R., Literature Search: T.S., Writing: T.S., H.L., W.W.

Conflict of Interest: No conflict of interest was declared by the authors.

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