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Research Article

Evaluation of Amikacin Regimens, C_{max}/MIC Ratios, and Clinical Outcomes in a Hospital at Yogyakarta, Indonesia

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Abstract

Amikacin is widely used to treat infections caused by Gram-negative bacteria. Its narrow therapeutic range necessitates plasma concentration monitoring through Therapeutic Drug Monitoring (TDM). However, limited infrastructure has restricted TDM implementation in many Indonesian healthcare settings. This study aims to evaluate amikacin dosing, estimate blood concentrations using pharmacokinetic equations, assess the pharmacokinetic/pharmacodynamic (PK/PD) profile, and analyze clinical outcomes. This descriptive-analytic study employed a retrospective cross-sectional design. It was conducted at a hospital in Yogyakarta by collecting data on amikacin dosing regimens, patient clinical outcomes, serum creatinine levels, and antibiotic sensitivity test results. The study subjects were hospitalized patients with infections who received amikacin therapy. Descriptive analysis was performed on patient characteristics, while estimated blood drug levels and PK/PD profiles were calculated using pharmacokinetic formulas and analyzed descriptively. A total of 44 amikacin dosing regimens from 40 patients met the inclusion and exclusion criteria. Of these, 39 regimens were appropriate according to dosing guidelines, and 26 (66.7%) resulted in favorable clinical outcomes. In contrast, five inappropriate regimens were associated with poor clinical outcomes. Among the 39 appropriate regimens, only 18 (46.2%) achieved the target peak plasma concentration (C_{max}). Furthermore, of these 18 regimens, only two (11.1%) achieved the target C_{max}/MIC ratio, with one associated with a favorable clinical outcome and one without improvement. These findings suggest that, despite appropriate dosing, most amikacin regimens failed to achieve the optimal C_{max}/MIC ratio required for effective clinical outcomes, highlighting the potential value of TDM and individualized dosing strategies to optimize amikacin therapy.

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INTRODUCTION

Infectious diseases caused by pathogenic microorganisms remain a major public health concern worldwide, particularly in developing nations[1]. Management of bacterial infections relies heavily on rational antibiotic therapy to optimize clinical recovery while mitigating the global emergence of antimicrobial resistance[2]. Among the available antibacterial agents, aminoglycosides are among the earliest established classes and maintain widespread clinical utility due to low rates of resistance and broad-spectrum bactericidal activity against aerobic Gram-negative bacilli[3]. Structurally composed of amino sugars connected by glycosidic linkages, aminoglycosides exert their bactericidal effect by binding to the 30S ribosomal

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subunit to inhibit bacterial protein synthesis. Furthermore, the pharmacokinetic characteristics of aminoglycosides are among the most thoroughly investigated in clinical pharmacology[4].

Despite their clinical utility against Gram-negative infections, aminoglycosides carry a well-documented risk of nephrotoxicity, necessitating precise dosage individualization in patients with impaired renal function. Compromised renal clearance alters both drug distribution and elimination, predisposing patients to drug accumulation, elevated systemic exposure, and increased toxicity at standard doses. Additionally, pharmacodynamic alterations in renal impairment can unpredictably shift the therapeutic window, predisposing patients to either therapeutic failure or enhanced drug toxicity[5]. Consequently, amikacin, a key broad-spectrum aminoglycoside, requires therapeutic drug monitoring (TDM) to track serum concentrations, ensure therapeutic efficacy, and prevent dose-dependent adverse events[6,7]. However, routine TDM implementation remains limited in resource-constrained healthcare settings across Indonesia[8]. In the absence of routine serum drug-level assays, mathematical pharmacokinetic equations provide a vital alternative for estimating systemic amikacin exposure and verifying whether calculated peak concentrations meet target minimum inhibitory concentration (MIC) thresholds[9]. For most susceptible Gram-negative pathogens, the baseline MIC for amikacin is designated at less than 8 µg/mL. Because amikacin exhibits concentration-dependent bactericidal activity, its clinical efficacy is primarily governed by the peak concentration-to-MIC (C_{max}/MIC) ratio, with optimal bacterial clearance requiring a C_{max}/MIC ratio of at least 8- to 10-fold[10].

Evaluations of aminoglycoside utilization in Indonesian hospitals reveal persistent challenges regarding irrational dosing practices. For example, Rouchmana *et al*.[8] reported that 46.25% (n = 37/80) of hospitalized patients receiving amikacin in Yogyakarta were prescribed inappropriate dosage regimens. Moreover, clinical studies linking estimated pharmacokinetic/pharmacodynamic (PK/PD) parameters to patient outcomes in Indonesia remain scarce. Suryoputri *et al*.[11] observed that while 96.3% (n = 52/54) of pediatric pneumonia patients treated with gentamicin at Ajibarang Hospital achieved average steady-state concentrations ($C_{ss,avg}$) within the therapeutic range (0.5–10 mg/L), only 40.4% (n = 21/52) of those within range showed definitive clinical improvement. Similarly, Nabila *et al*.[12] evaluated amikacin and gentamicin PK/PD targets in a pediatric intensive care unit (PICU) at Dr. Sardjito Hospital in Yogyakarta, finding that 74% (n = 17/23) of amikacin recipients and 46% (n = 16/35) of gentamicin recipients achieved target C_{max}/MIC ratios. Another neonatal intensive care unit (NICU) evaluation demonstrated that among 86 neonates treated with amikacin achieving a C_{max}/MIC ratio $\geq$ 10, only 15.10% (n = 13/86) exhibited positive clinical responses[13]. Importantly, these previous Indonesian evaluations were strictly limited to pediatric and neonatal cohorts. Data detailing amikacin PK/PD target attainment and its direct impact on clinical outcomes across wider, non-pediatric inpatient populations remain scarce, particularly in facilities where routine TDM is unavailable. Therefore, this study was designed to evaluate the appropriateness of amikacin dosing regimens, estimate systemic amikacin exposure using established pharmacokinetic equations, assess C_{max}/MIC target attainment, and examine its relationship with clinical outcomes across a broader, diverse inpatient population.

MATERIALS AND METHODS

Materials

The primary data materials for this study comprised retrospective clinical variables extracted directly from electronic medical records, including individual amikacin dosage regimens, patient anthropometric measurements (body weight and height), baseline serum creatinine levels, microbiological culture findings, and antimicrobial susceptibility test profiles. To evaluate the clinical appropriateness of the prescribed dosage regimens, standard tertiary pharmaceutical literature and clinical practice references were used as benchmark criteria, specifically Lexicomp, Drug Doses, and the Injectable Drug Guide. Furthermore, to evaluate the pharmacodynamic effectiveness of amikacin in achieving target C_{max}/MIC exposure ratios, bacterial MIC thresholds were assigned using standardized epidemiological cutoff values established by the Clinical and Laboratory Standards Institute (CLSI) 2024 guidelines[14]. All extracted demographic, laboratory, and pharmacological data were systematically recorded and organized using a standardized, structured data collection instrument to facilitate subsequent pharmacokinetic modeling and clinical analysis.

Methods

Study design, setting, and ethical approval

This study employed a descriptive and analytical observational design with a retrospective cross-sectional framework. Data collection was performed between April and May 2024 by reviewing archived electronic medical records of inpatients treated at a tertiary referral hospital in Yogyakarta, Indonesia, during the observation period from January to December 2023. Ethical approval was obtained from the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (Ethical Clearance Approval Certificate No. KE/FK/1602/EC/2023).

Study population and eligibility criteria

The study population comprised all hospitalized patients diagnosed with bacterial infections who received intravenous amikacin therapy during the 2023 calendar year. Eligible participants were selected using a total sampling based on predefined criteria. Inclusion criteria comprised hospitalized patients of all age groups receiving intravenous amikacin therapy for at least 72 consecutive hours who had complete demographic, clinical, dosing, and laboratory documentation in their electronic medical records. Patients were excluded if their clinical illness trajectory could not be completely tracked, if they received active hemodialysis or renal replacement therapy during amikacin administration, or if their total hospital length of stay exceeded 45 days[15].

Data collection and clinical outcome assessment

Retrospective clinical variables were systematically extracted using a structured data collection sheet, including patient demographics, body weight, height, diagnosis, amikacin dose, dosing interval, infusion duration, baseline serum creatinine, leukocyte counts, procalcitonin levels, chest X-ray findings, and microbiological culture profiles. Clinical outcomes were evaluated at the completion of amikacin therapy and categorized as either improved or not improved. An improved clinical outcome was defined as documented resolution of clinical symptoms specific to the primary infection site, along with favorable normalization of objective parameters, including temperature stabilization, declining leukocyte or procalcitonin levels, radiological improvement, or explicit physician progress notes confirming a therapeutic response. A non-improved clinical outcome was defined as clinical stasis, symptom exacerbation, lack of biomarker or radiological progress, escalation to secondary rescue antibiotics due to treatment failure, or inpatient mortality.

Data analysis

Descriptive statistical analyses were performed to summarize patient demographic characteristics, clinical baseline variables, dosage regimen parameters, and qualitative classifications of dosing appropriateness. Continuous variables were expressed as mean values with standard deviations or medians with interquartile ranges, whereas categorical variables were summarized as absolute frequencies and percentages.

To evaluate individual pharmacodynamic exposure, predictive $C_{ss,max}$, and trough ($C_{ss,min}$) amikacin concentrations were calculated using standard one-compartment linear pharmacokinetic models. Population pharmacokinetic estimates for volume of distribution (V_d) and elimination half-life ($t_{½}$) were derived from validated tertiary clinical pharmacology literature, adjusted for patient renal clearance (estimated via the Cockcroft-Gault or Bedside Schwartz formulas). For intravenous bolus administration, steady-state peak and trough concentrations were calculated using **Equations 1** and **2**. For intermittent intravenous infusion administration (where t represents infusion duration), steady-state concentrations were calculated using **Equations 3** and **4**, where D represents the amikacin dose per administration in milligrams, V_d denotes the individual volume of distribution in liters, k indicates the elimination rate constant derived from 0.693 / $t_{½}$ in hours^{-1}, τ represents the dosing interval in hours, and t indicates the intravenous infusion time in hours.

$$C_{ss,max} = \frac{D}{Vd \times (1 - e^{-k \times \tau})} \quad [1]$$

$$C_{ss,min} = C_{ss,max} \times e^{-k \times \tau} \quad [2]$$

$$C_{ss,max} = \frac{D}{t \times k \times V_d} \times \frac{1 - e^{-k \times t}}{1 - e^{-k \times \tau}} \quad [3]$$

$$C_{ss,min} = C_{ss,max} \times e^{-k \times (\tau - t)} \quad [4]$$

The calculated $C_{ss,max}$ was subsequently divided by the assigned microbial MIC threshold to determine individual C_{max}/MIC ratios. Target C_{max}/MIC attainment was defined as a ratio ≥8-10. Bivariate statistical analysis was executed to evaluate the association between calculated C_{max}/MIC target attainment (achieved vs. non-achieved) and patient clinical outcomes (improved vs. non-improved) using Fisher's Exact Test. All statistical tests were two-tailed, with statistical significance set at $p < 0.05$. Statistical computations were performed using SPSS and Microsoft Excel.

RESULTS AND DISCUSSION

Out of 117 hospitalized patients who received intravenous amikacin therapy between January and December 2023 at a hospital in Yogyakarta, 77 patients were excluded based on predefined criteria: 15 received active hemodialysis, 29 had incomplete medical record documentation, 6 received amikacin outside the designated observation timeframe, and 27 had total hospital lengths of stay exceeding 45 days. Consequently, 40 unique patients were included in the final analytical cohort. The demographic, clinical, and microbiological characteristics of the study cohort are presented in **Table I**. Male patients accounted for 57.5% (n = 23) of the cohort, consistent with global epidemiological literature reporting higher rates of severe infection-related hospitalizations among males[16]. Sex-based immunological differences, influenced by hormonal regulation and X-chromosome gene expression, modulate pathogen susceptibility and inflammatory responses[17]. Furthermore, behavioral risk factors, including higher historical rates of tobacco and alcohol consumption among men, contribute to an elevated incidence of severe lower respiratory tract infections[18,19]. Older adults aged >65 years comprised half of the study population (50.0%, n = 20), while adults aged 18–65 years accounted for 40.0% (n = 16), and pediatric patients (<18 years) represented 10.0% (n = 4). The high proportion of elderly patients highlights age-associated immunosenescence and a greater burden of chronic comorbidities, which increase susceptibility to invasive infections caused by Gram-negative bacteria[20].

Table I. Baseline characteristics of patients receiving intravenous amikacin therapy (n = 40).

Patient Characteristic	Sub-category / Variable	Patient Frequency (n)	Percentage (%)
Gender	Male	23	57.5
	Female	17	42.5
Age Group (years)	<18	4	10.0
	18–65	16	40.0
	>65	20	50.0
Amikacin Dosing Regimen	Single daily dose (Extended-interval)	34	85.0
	Multiple daily doses (Traditional)	6	15.0
Hospital Length of Stay (days)	3–10	1	2.5
	11–25	21	52.5
	26–40	12	30.0
	>40	6	10.0
Inpatient Care Unit	Intensive Care Unit (ICU)	22	55.0
	General Inpatient Ward (Non-ICU)	18	45.0
Isolated Pathogenic Bacteria	*Acinetobacter baumannii*	17	42.5
	Acinetobacter baumannii + Pseudomonas aeruginosa	2	5.0
	Acinetobacter baumannii + Escherichia coli	2	5.0
	Acinetobacter baumannii + Klebsiella pneumoniae	1	2.5
	Acinetobacter baumannii + Citrobacter freundii	1	2.5
	Acinetobacter baumannii + Pseudomonas aeruginosa + Klebsiella pneumoniae	1	2.5
	Escherichia coli	4	10.0
	Escherichia coli + Proteus mirabilis	2	5.0
	Escherichia coli + Pseudomonas aeruginosa	1	2.5
	Pseudomonas aeruginosa	3	7.5
	Pseudomonas aeruginosa + Proteus mirabilis	1	2.5
	Klebsiella pneumoniae	2	5.0
	Klebsiella pneumoniae + Enterobacter cloacae	1	2.5
	Enterobacter cloacae	2	5.0

Single daily dosing (extended-interval dosing) was administered to 85.0% (n = 34) of patients, whereas 15.0% (n = 6) received traditional multiple-daily-dose regimens. Extended-interval aminoglycoside dosing leverages concentration-dependent bactericidal activity and the post-antibiotic effect (PAE) to optimize bacterial clearance while reducing accumulation in renal cortical cells and inner-ear endolymph, thereby mitigating the risks of nephrotoxicity and ototoxicity[21]. Over half of the cohort (52.5%, n = 21) experienced hospital stays of 11 to 25 days, with 40.0% remaining hospitalized for >25 days. Prolonged hospitalization reflects the severity of underlying disease, the ICU management requirements, and the complexity of treatment courses for hospital-acquired infections. Critically ill patients managed in the ICU represented 55.0% (n = 22) of the study population, underscoring the role of amikacin as a key agent against multidrug-resistant (MDR) Gram-negative pathogens in intensive care settings[21]. Among isolated pathogens, *A. baumannii* was the predominant causative organism, identified in 60.0% (n = 24) of total cases, either as a monomicrobial infection (42.5%) or as part of a polymicrobial infection.

Across the 40 study patients, a total of 44 distinct amikacin dosing regimens were evaluated. The distribution of treatment durations is summarized in **Table II**. The majority of amikacin regimens (43.2%, n = 19) were administered for 4 to 7 days, aligning with clinical guidelines recommending 5 to 7 days of therapy for uncomplicated hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and complicated urinary tract infections[22,23]. Clinical response to appropriate antibiotic therapy is typically observable within 48 to 72 hours of treatment initiation[22]. Within the 4–7 days cohort, 3 patients discontinued amikacin on day 4 due to rapid clinical deterioration or inpatient mortality, whereas the remaining patients completed full 5- to 7-day courses. Extended courses (> 7 days) were prescribed in 40.9% (n = 18) of regimens, primarily for severe polymicrobial infections, delayed clinical response, or deep-seated infection foci.

Table II. Treatment duration across evaluated amikacin regimens (n = 44).

Amikacin Treatment Duration	Regimen Frequency (n)	Percentage (%)
3 days	7	15.9
4–7 days	19	43.2
8–14 days	14	31.8
>14 days	4	9.1
Total	**44**	**100.0**

Individual renal clearance was calculated using the Cockcroft-Gault equation for adults and the Bedside Schwartz formula for pediatric patients. According to KDIGO 2024 Clinical Practice Guidelines for Chronic Kidney Disease[24], 16 patients exhibited normal renal function, whereas 24 patients demonstrated varying degrees of renal impairment: mild (n = 8), mild-to-moderate (n = 7), moderate-to-severe (n = 5), and severe impairment (n = 4). No patients were in end-stage renal failure. Evaluating amikacin dosage, administration frequency, and treatment duration against tertiary drug references (Lexicomp, Drug Doses, Injectable Drug Guide) revealed that 88.6% (n = 39) of prescribed regimens were appropriate, while 11.4% (n = 5) were inappropriate due to incorrect dosing or inappropriate administration intervals relative to renal function.

The association between the appropriateness of amikacin dosing and clinical outcomes is presented in **Table III**. Among the 39 appropriate amikacin regimens, 66.7% (n = 26) resulted in improved clinical outcomes, confirming that guideline-concordant dosing supports therapeutic success. Conversely, all 5 inappropriate regimens (100.0%) resulted in non-improved outcomes. However, 13 patients receiving appropriate dosing failed to improve, indicating that clinical recovery is influenced by factors beyond dosing accuracy, such as severe underlying comorbidities, immunosuppression, or altered pharmacokinetic parameters that impair local tissue penetration[25].

Table III. Evaluation of amikacin dosing regimen appropriateness vs. patient clinical outcomes (n = 44).

Dosing Appropriateness Category	Improved Clinical Outcome (n, %)	Non-Improved Clinical Outcome (n, %)	Total Regimens (n, %)
Appropriate Regimen	26 (66.7%)	13 (33.3%)	39 (88.6%)
Inappropriate Regimen	0 (0.0%)	5 (100.0%)	5 (11.4%)
Total	**26 (59.1%)**	**18 (40.9%)**	**44 (100.0%)**

Predictive $C_{ss,max}$ were calculated for the 39 appropriate amikacin regimens using standard population pharmacokinetic formulas. Predicted C_{max} values were evaluated against established therapeutic targets: 55–64 µg/mL for single-daily dosing and 15–40 µg/mL for multiple-daily dosing regimens. The results of C_{max} target attainment are summarized in **Table IV**. Over half of the evaluated regimens (53.8%, n = 21) failed to achieve predicted C_{max} therapeutic targets. This high rate of

non-attainment is largely attributable to physiological alterations in critically ill ICU patients, who comprised 55.0% of the cohort. Critical illness alters fluid balance, vascular permeability, protein binding, and extracellular fluid volume, leading to an expanded V_d that exceeds the standard baseline population parameter of 0.25 L/kg used in predictive calculations[26]. Underestimating V_d in septic or fluid-resuscitated patients leads to overestimating predicted serum levels, masking subtherapeutic exposure in clinical practice[27].

Table IV. Predicted amikacin C_{max} target attainment (n = 39).

Peak Concentration (C_{max}) Attainment	Frequency (n)	Percentage (%)
Target Achieved	18	46.2
Target Not Achieved	21	53.8
Total	**39**	**100.0**

For the 18 amikacin regimens that achieved target C_{max} levels, pharmacodynamic efficacy was evaluated by calculating individual C_{max}/MIC ratios using CLSI 2024 epidemiological cutoff MIC values for identified bacterial pathogens. Target PK/PD exposure was defined as achieving a C_{max}/MIC ratio > 8-10. The relationship between C_{max}/MIC target attainment and patient clinical outcomes is summarized in **Table V**. Only 2 of the 18 regimens (11.1%) achieved the target C_{max}/MIC ratio of ≥ 8-10. Among these 2 regimens, 1 patient experienced clinical improvement, while the other did not. Conversely, 16 regimens (88.9%) failed to achieve the C_{max}/MIC target; nevertheless, 37.5% (n = 6) of these non-attaining regimens still resulted in clinical recovery. Clinical improvement despite unachieved C_{max}/MIC targets may occur because true local strain MICs are lower than the conservative CLSI 2024 epidemiological cutoff values used in predictive calculations[28,29]. Additionally, concurrent broad-spectrum antibiotic therapy can produce synergistic antibacterial effects, as observed in patients receiving amikacin in combination with ceftazidime for polymicrobial pneumonia caused by *A. baumannii* and *P. aeruginosa*[30].

Table V. Pharmacodynamic C_{max}/MIC target attainment vs. clinical outcomes (n = 18).

Pharmacodynamic C_{max}/MIC Target Attainment	Improved Clinical Outcome (n, %)	Non-Improved Clinical Outcome (n, %)	Total Regimens (n, %)
Target Achieved (C_{max}/MIC ≥ 8-10)	1 (50.0%)	1 (50.0%)	2 (11.1%)
Target Not Achieved (C_{max}/MIC < 8-10)	6 (37.5%)	10 (62.5%)	16 (88.9%)
Total	**7 (38.9%)**	**11 (61.1%)**	**18 (100.0%)**

Bivariate statistical analysis evaluating the association between predicted C_{max}/MIC target attainment and clinical outcomes yielded no statistically significant correlation (Fisher's Exact Test, $p = 1.000$, $\alpha = 0.05$). This lack of statistical significance indicates that predicted C_{max}/MIC values alone do not reliably predict clinical recovery in this cohort. This finding is likely influenced by sample size constraints, the reliance on population-derived pharmacokinetic constants rather than direct TDM serum assays, and the absence of strain-specific MIC values.

This study has several limitations. First, pharmacokinetic parameters (V_d and $t_{½}$) were estimated using standard population equations rather than being measured directly via TDM. These predictive models may not fully capture pharmacokinetic alterations in critically ill ICU patients, such as capillary leak, fluid shifts, or augmented renal clearance. Second, bacterial MICs were assigned using CLSI 2024 breakpoint standards rather than measured strain-specific MICs for clinical isolates. Finally, the relatively small sample size (n = 40) limits statistical power and generalizability. Prospective studies incorporating direct serum amikacin concentration assays and isolate-specific MIC determinations are recommended to refine aminoglycoside dosing protocols in Indonesian hospitals.

CONCLUSION

In conclusion, this study demonstrates that guideline-appropriate amikacin dosing regimens do not consistently achieve target C_{max}/MIC ratios or guarantee favorable clinical outcomes, particularly in critically ill populations with altered pharmacokinetic profiles. Consequently, implementing routine TDM and individualizing dosage regimens are essential strategies to optimize amikacin exposure, prevent therapeutic failure, and enhance clinical outcomes.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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