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Original Article

Therapeutic Drug Monitoring of Amikacin in Hospitalized Patients: Outcomes from a Teaching Hospital of Hanoi University of Pharmacy

Nguyen Thi Dua[1], Tran Thi Cat Khanh[2], Vu Thi Ngoc Mai[2], Nguyen Duc Long[1], Tran Phuong Nga[2], Do Pham Minh Chau[2], Dinh Tra My[2], Le Minh Hiep[2], Tran Thi Thu Thuy[1], Phan Thi Linh[1], Nguyen Trong Hao[1], Nguyen Thi Huyen Thu[1], Tran Thi Thu Trang[2], Nguyen Thi Lien Huong[2], Nguyen Tu Son[2], Nguyen Thanh Hai[2], Le Ba Hai[2,*]

[1]*Saint Paul General Hospital, 12 Chu Van An, Ba Dinh, Hanoi, Vietnam*

[2]*Hanoi University of Pharmacy, 13-15 Le Thanh Tong, Cua Nam, Hanoi, Vietnam*

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Abstract: Background: Amikacin is an aminoglycoside antibiotic widely used in the management of multidrug-resistant Gram-negative infections. However, its clinical use poses significant challenges due to a narrow therapeutic window, interpatient pharmacokinetic variability, and potential nephrotoxicity and ototoxicity. Therefore, implementation of Therapeutic Drug Monitoring (TDM) of amikacin is considered essential to optimize dosing regimens and ensure both efficacy and safety. Method: A prospective, descriptive study on hospitalized adult patients receiving TDM for amikacin. Patients undergoing dialysis and those lacking accurate or clearly documented sampling time data were excluded from the analysis. Blood samples were collected to estimate peak (Cpeak) and trough (Ctrough) concentrations using a Bayesian pharmacokinetic approach (Precise PK^{Rx}). The PK/PD targets for therapeutic efficacy and safety were defined as Cpeak/MIC ≥ 8 µg/mL and Ctrough ≤ 2 µg/mL. Results: From August 2024 to May 2025, a total of 45 patients were enrolled in the study, with a median age of 69 years, of whom 64.4% were treated in the intensive care unit (ICU). Amikacin was most frequently prescribed for pneumonia (53.3%) and sepsis/septic shock (35.6%). The predominant pathogens isolated were *Klebsiella pneumoniae* (38.0%) and *Escherichia coli* (16.0%). The median initial dose of amikacin was 20 mg/kg [IQR: 7.6 - 32.5]. The mean number of TDM occasions per patient was 1.9 ± 1.1. After the first TDM, 46.7%

* Corresponding author.
E-mail address: hailb@hup.edu.vn

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of patients achieved the target Cpeak, and 82.2% achieved the target Ctrough. The attainment rate for the efficacy target improved from 46.7% after the first TDM to 100% after the fourth and fifth TDM assessments. The target attainment rate for safety remained consistently above 80%. Conclusion: Optimization of amikacin dosing through TDM should be routinely implemented and considered in other hospitals to ensure both efficacy and safety in the treatment of severe multidrug-resistant infections.

Keywords: Amikacin, Therapeutic Drug Monitoring (TDM), Multidrug-Resistant Bacteria, Dose Optimization, High-Dose Amikacin.

1. Introduction

Amikacin, a widely used aminoglycoside antibiotic, remains today a critical agent in the treatment of Gram-negative bacteria infections, particularly multidrug-resistant strains. However, its clinical application poses substantial challenges due to significant interindividual pharmacokinetic variability, a narrow therapeutic window, and the risk of nephrotoxicity and ototoxicity. In critically ill patients, pathophysiological changes further complicate the prediction of drug concentrations and dose adjustments. According to Decision No. 5631/QĐ-BYT issued by the Vietnamese Ministry of Health [1], the use of aminoglycosides requires close monitoring and individualized dosing. Amikacin exhibits concentration-dependent bactericidal activity, and achieving the efficacy (Cpeak/MIC $\geq$ 8) is considered essential for therapeutic efficacy. Simultaneously, to minimize drug accumulation and toxicity, particularly nephrotoxicity byadjusting dosing intervals to maintain a low trough concentration (Ctrough) is necessary [2].

In this context, TDM serves as an effective strategy to guide individualized therapy and reduces the risk of toxicity [3]. Dosing adjustment based on TDM results has been recommended and routinely implemented in clinical practice at various international healthcare institutions, including Stanford University Hospital [4], the Queensland hospital system [5], and many others. In Vietnam, several healthcare facilities such as Bach Mai Hospital and the University Medical Center Ho Chi Minh City have also initiated the implementation of TDM protocols for amikacin [6, 7].

At Saint Paul's General Hospital - a Grade I hospital belonging the Hanoi Department of Health isaffiliated with a key clinical training site of Hanoi University of Pharmacy, amikacin is frequently prescribed in the ICU and Surgical departments [8]. While TDM for vancomycin has been implemented across several patient populations in our hospital, TDM for amikacin has not yet been routinely adopted. In response to clinical demand, starting from August 15, 2024, in collaboration with experts from Hanoi University of Pharmacy, the hospital developed and launched a TDM protocol for amikacin in adult patients. This study was conducted to *analyze the outcomes of implementing amikacin TDM sessions at Saint Paul's General Hospital*, thereby providing a foundation for the broader application and scaling of the TDM model to other affiliated teaching hospitals of the University.

2. Subjects and Methods

2.1. Study Subjects

The study included inpatients at Saint Paul's General Hospital from August 2024 to May 2025, who received at least one dose of intravenous amikacin and had an indication for TDM according to the hospital's protocol. Patients under 18 years of age or those lacking data on the timing of drug administration and blood sampling were excluded from the analysis.

2.2. Methods

A prospective descriptive study was conducted based on the treatment process and therapeutic drug monitoring (TDM) of amikacin

Blood samples were collected at designated time points in accordance with the protocol and analyzed at the Laboratory Center of Saint Paul's General Hospital. Upon obtaining TDM results, we evaluated target attainment and proposed dose adjustments when necessary. Measured plasma concentrations were input into the Bayesian software (PrecisePK^{RX}) to estimate attainment of the efficacy target Cpeak/MIC (8 - 10) and safety target Ctrough (<2 µg/mL). In case of pathogens were isolated, the minimum inhibitory concentration (MIC) of amikacin was determined by using the E-test method in accordance with the 2024 Clinical and Laboratory Standards Institute (CLSI) guidelines [9].

Renal function was evaluated by using the Cockcroft - Gault formula [10]. Acute kidney injury (AKI) cases were classified based on the KDIGO staging criteria issued in 2012 [11].

Ethics Statement: Researchers did not intervene in the patient's treatment process. The study was conducted following the approval of the project titled "*Implementation of Therapeutic Drug Monitoring of Amikacin in Patients Treated at Saint Paul's General Hospital*", granted by the Scientific Committee of Saint Paul's General Hospital and the Hanoi Department of Health, under Decision No. 1433–QĐ-BVXP and 3548–QĐ-SYT

3. Results

3.1. Patient Population Characteristics and Amikacin Utilization Profile

Within August 2024 and May 2025, 45 patients meeting the inclusion and exclusion criteria were enrolled in the study. The demographic and clinical characteristics of the patient population, along with details of amikacin administration, are presented in Table 1.

Table 1. Patient population characteristics and amikacin utilization profile

Variables	Number and average (N = 45)
Sex, n (%)	
Male	25 (55.6 %)
Female	20 (44.4%)
Age (years)*	69 (61 - 82)
Distribution, n (%)	
18-60	10 (22.2%)
≥ 60	35 (77.8%)
Body Mass Index (kg/m^2), n (%)	
Underweight (dưới 18.5)	9 (20.0%)
Normal (18.5 - 24.9)	33 (73.3%)
Overweight (25.0 - 29.9)	3 (6.7%)
Most recent renal function before amikacin initiation - ClCr (ml/min)*	
Distribution, n (%)	53.0 (35.7 - 72.6)
- 50	
-130	20 (44.4%)
>130	23 (51.1%)
	2 (4.4%)
Distribution of patients by department, n (%)	
Emergency and Intensive Care Department	*31 (68.8%)*
Surgical ICU	9 (20.0%)
Medical ICU	20 (44.4%)
Emergency Department	2 (4.4%)
Surgical Department Cluster	*11 (24.4%)*

Variables	Number and average (N = 45)
Gastrointestinal Surgery (Digestive Surgery)	9 (20.0%)
Urology Surgery	2 (4.4%)
Medical Department Cluster	*1 (2.2%)*
General Internal Medicine I	1 (2.2%)
High-Tech Center	*1 (2.2%)*
Distribution of infection-related indications, n (%)	
Respiratory tract infections	24 (53.3%)
Gastrointestinal infections	16 (35.5%)
Bloodstream infections	9 (20.0%)
Septic shock	7 (15.6%)
Urinary tract infections	6 (13.3%)
Soft tissue infections	1 (2.2%)
Central nervous system infections	1 (2.2%)
Characteristics of Amikacin Use	
Initial dose administered (mg/kg)*	20,0 (15.6 - 23.1)
Distribution, n (%)	
< 15 mg/kg	7 (15.5%)
15 - <20 mg/kg	12 (26.7%)
20 - <25 mg/kg	18 (40.0%)
25 - 30 mg/kg	7 (15.5%)
>30 mg/kg	1 (2.2%)
*: Median, IQR	

The majority of patients were treated in the ICU (68.8%) and had respiratory tract infections (53.3%), gastrointestinal infections (35.5%), or bloodstream infections and septic shock (35.6%). More than 40% of patients had impaired renal function, with a ClCr below 50 mL/min. Notably, a large proportion of patients (57.8%) were initially prescribed an amikacin dose greater than 20.0 mg/kg.

3.2. Microbiological Characteristics

Among the 45 patients included in the study, 42 (93.3%) underwent microbiological culture. Pathogens were identified in 29 cases, yielding a total of 46 isolates. The majority of isolates were Gram-negative bacteria (93.5%), with *Klebsiella pneumoniae* (41.3%), *Escherichia coli*, and *Acinetobacter baumannii* (each 17.4%) being the most frequently isolated species. *K. pneumoniae* remained susceptible to amikacin in 66.7% of isolates; 94.5% had a MIC ≤ 8 µg/mL. *E.coli* showed full susceptibility (MIC = 4 µg/mL), whereas *A. baumannii* exhibited a high resistance rate (85.7%).

Among the 18 *K. pneumoniae* isolates with available antimicrobial susceptibility testing, only 22% were susceptible to carbapenems, 11% to piperacillin/tazobactam, and 6% to third-generation cephalosporins. Notably, 66.7% of the isolates remained susceptible or intermediate to aminoglycosides, and 8 isolates (44.4%) were susceptible or intermediate exclusively to amikacin.

3.3. Results of TDM of Amikacin

A total of 85 TDM sessions were conducted for 45 patients in the study sample. Among these, 24 patients (53.3%) underwent only one TDM session, while the remaining patients were monitored between two and five times. A total of 83 peak concentration samples (Sample 1, used to estimate Cpeak) and 76 trough concentration samples (Sample 2, used to estimate Ctrough) were collected. The average number of TDM sessions per patient was 1.9 ± 1.1. Regarding the timing of the first TDM session, the majority

were performed after the first dose of amikacin (34 patients, 75.6%). A smaller proportion of patients had samples taken after the second dose (6.7%) or later doses (3rd to 9th), ranging from 2.2% to 4.4%. Table 2 summarizes the distribution of TDM frequency in our study.

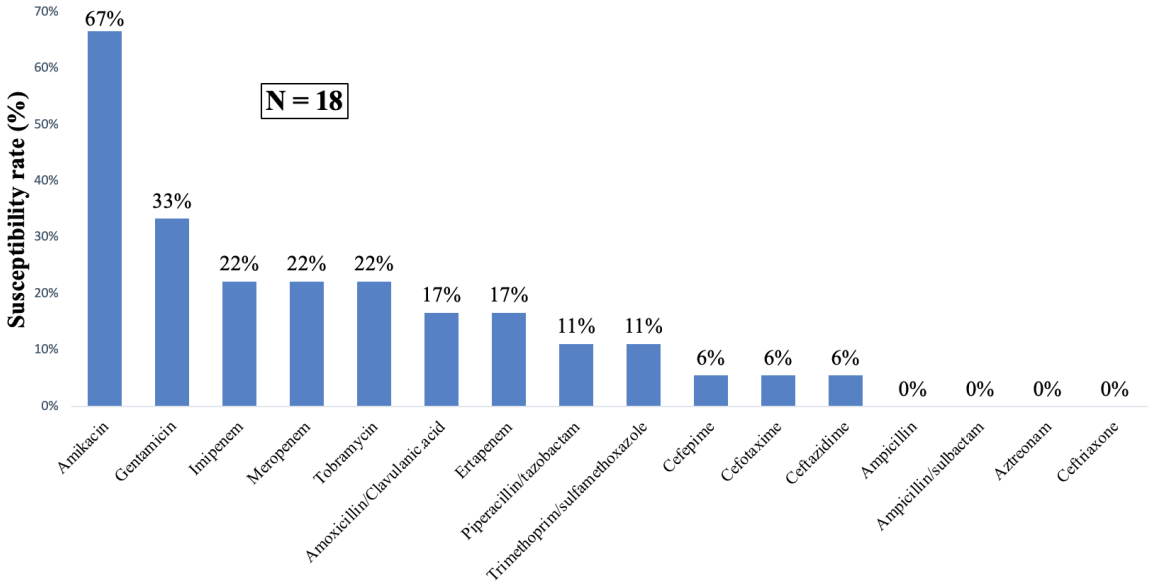

Figure 1. Antimicrobial susceptibility profile of *Klebsiella pneumoniae* to amikacin.

Table 2. Characteristics of amikacin TDM

Variables	Values (N = 45)
Number of patients undergoing TDM, n (%)	
TDM once	24 (53.3%)
TDM twice	8 (17.7%)
TDM three times	8 (17.7%)
TDM four times	4 (8.9%)
TDM five times	1 (2.2%)
Number of samples*, n	
Sample 1	83
Sample 2	76
Mean number of TDM sessions per patient, (mean ± SD chuẩn) (min-max)	1.9 ± 1.1 (1 - 5)

After the first TDM session, 46.7% of patients reached the Cpeak/MIC target, while 82.2% reached the Ctrough target. Among 21 patients had a second TDM session, the rate of reaching the Cpeak/MIC target increased to 57.1%, and the Ctrough target to 95.2%. These proportions continued to increase with the third and fourth TDM sessions. In the fifth session (only one patient), 100% target attainment was recorded for both Cpeak/MIC and Ctrough (Figure 2).

Regarding dose adjustment trends, common approaches included increasing the dose or adjusting the dose interval - most frequently by extending the interval. Dose reductions were rarely implemented. In the first TDM session, 44% of patients had no dose change, while 33% had dose increases. The proportion of dose

increases gradually declined in subsequent sessions: by the third TDM, only 25% had dose increases, and by the fourth and fifth sessions, all patients (100%) maintained their current dose.

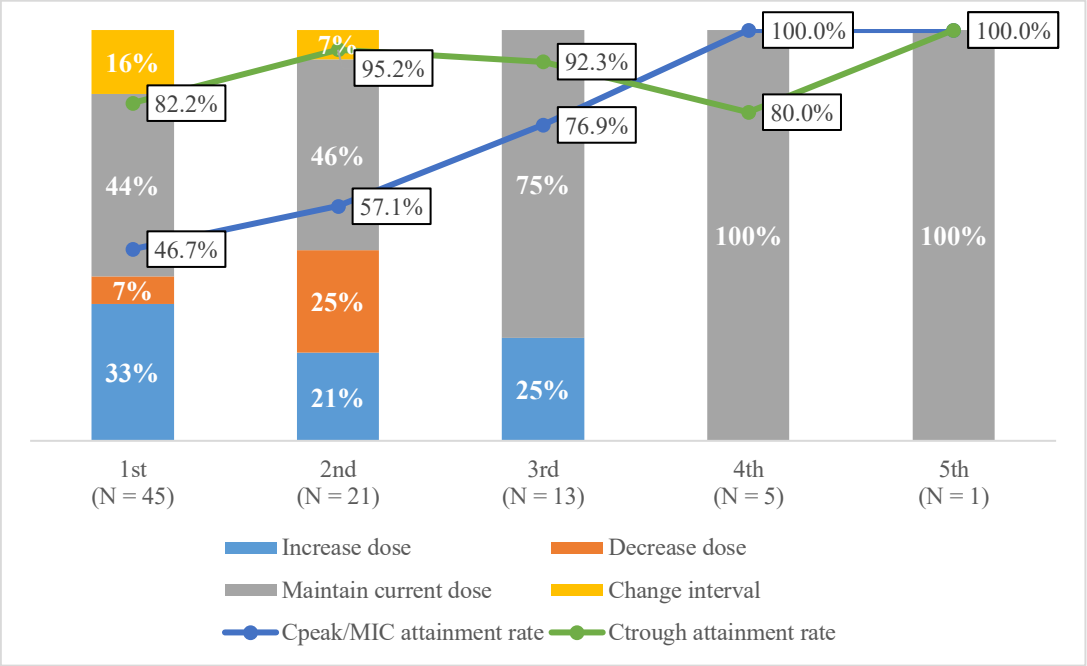

Figure 2. Trends in Cpeak/MIC and Ctrough target attainment and dose adjustments after each TDM sessions.

3.4. Renal Toxicity Risk Characteristics

Table 3 presents the characteristics associated with the risk of nephrotoxicity in patients receiving amikacin. In total, 88.9% of patients underwent serum creatinine testing during treatment.

Table 3. Renal toxicity risk characteristics

Variables		Values
Proportion of patients tested for creatinine before and during amikacin use, n (%, N = 45)		40 (88.9%)
Proportion of patients diagnosed with AKI during treatment, n (%, N = 40)		8 (20.0%)
Proportion of patients with AKI by KDIGO stage, n (%, N = 40)	Stage 1	7 (87.5)
	Stage 2	0 (0.0%)
	Stage 3	1 (12.5%)
Time from amikacin initiation to AKI onset (day), median (IQR)		4 (3 - 8.25)
Proportion of patients tested for creatinine at both treatment start and end, n (%, N = 45)		35 (77.8%)
Median ClCr before treatment (ml/min), median (IQR)		49.8 (32.2 - 59.8)
Median ClCr after treatment (ml/min), median (IQR)		47.1 (30.5 - 72.0)

Among patients monitored for renal function during treatment, 8 (20.0%) had AKI according to KDIGO criteria. Most AKI cases were stage 1 (87.5%), with only one case (12.5%) progressing to stage 3. The median time from the start of amikacin treatment to AKI onset was 4 days

(IQR: 3 - 8.25). A total of 35 patients had serum creatinine measurements taken both within 24 hours before initiating amikacin and within 24 hours after discontinuation. A Wilcoxon signed-rank test showed no statistically significant difference in ClCr between these two time points.

4. Discussion

The patient population in this study was mostly elderly (77.8%) and treated in ICUs (68.8%). Factors including being overweight (6.7%), older age (77.8%), impaired renal function (44.4%), intensive care treatment (68.8%), and severe infections like sepsis and septic shock affect the pharmacokinetics of the drug, increasing interindividual variability in drug concentration. In such cases, TDM plays a crucial role in individualizing doses, optimizing treatment efficacy, and minimizing toxicity risks [12].

Regarding microbiological characteristics, most of the isolated bacteria were Gram-negative (93.5%), with the most common being *Klebsiella pneumoniae* (41.3%) and *Escherichia coli* (17.4%), consistent with findings from Nguyen Thanh Tam (2024) at Nhan Dan Gia Dinh Hospital [13]. All *E. coli* strains were sensitive to amikacin (MIC = 4 µg/mL), while 94.4% of *K. pneumoniae* strains had MIC ≤ 8 µg/mL, which fell within the range for dose optimization. Additionally, 8 out of 18 strains (44.4%) were resistant to all other antibiotics but remained sensitive or intermediate to amikacin, which shows amikacin's critical role in treating these bacteria and the need for dose optimization.

A total of 85 TDM sessions were conducted for 45 patients. After the first TDM session, only 46.7% of patients achieved the target Cpeak/MIC ratio, which is lower than the 80.4% reported by Kato et al. (2017) [14]. One possible reason is the relatively cautious initial dosing in our study, with a median dose of 20.0 mg/kg (range: 7.6 - 28.7). Although 57.8% of patients received doses above 20 mg/kg, most were still close to 20 mg/kg - lower than the initial dose of ≥25 mg/kg used in Kato's study [14]. This conservative approach may be due to the recent implementation of TDM at our hospital, where dosing guidelines recommend a range of 15 - 30 mg/kg. At Saint Paul Hospital, since amikacin is also widely used outside of ICUs, for example in surgical departments (59.9%), where 42% of patients received standard doses of 15 - 20 mg/kg [8], lower initial doses remain common for non-ICU patients with lower risk of resistant bacteria. The target Cpeak/MIC attainment rate improved markedly with each subsequent TDM: from the third TDM session onward, 76.9% of patients reached the effective threshold; from the fourth TDM onward, 100% of patients achieved the target. These results demonstrate the advantages of the PrecisePK software, which uses the Bayesian method to update individual pharmacokinetic parameters based on previous drug level, increasing estimation accuracy [15].

Regarding safety data, there was no statistically significant difference in the mean ClCr between the start and end of treatment, even though 44.4% of patients had pre-existing renal impairment (ClCr < 50 mL/min) and many had risk factors for nephrotoxicity (advanced age, prolonged treatment, use of nephrotoxic drugs). The observed rate of AKI was 20% (8/40 patients monitored), which is lower than the rates reported by Nguyen Thanh Tam (78.4%) [13] and Ngo Nguyen Nhat Anh (28.8%) [7]. This difference may be attributed to the significantly higher rate of Ctrough target attainment in our study (>80%), whereas the two aforementioned studies only achieved 62.95% and 64.30%, respectively, and used a higher Ctrough threshold (4 µg/mL compared to 2 µg/mL).

5. Conclusion

This study demonstrates that TDM of amikacin improves the achievement of PK/PD targets, with the rate of patients reaching efficacy target increasing progressively across TDM sessions: 46.7%, 57.1%, 76.9%, and reaching 100% from the fourth session onward.

Regarding safety target, there was no statistically significant difference in mean ClCr

between the start and end of treatment, despite patients having multiple risk factors for nephrotoxicity.

In conclusion, making amikacin TDM a routine practice and expanding its application to other hospitals would help ensure both efficacy and safety in the treatment of severe multidrug-resistant infections.

Acknowledgements

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