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ORIGINAL ARTICLE

EVALUATING SAFETY AND CLINICAL PHARMACOKINETICS OF POPULAR DOSAGE REGIMEN OF AMIKACIN IN PATIENTS WITH URINARY TRACT INFECTIONS

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ABSTRACT

Background: For all patients using aminoglycosides, a well-established concentration-effect relationship (toxicity) and medication monitoring is recommended. There are very few reports of therapeutic drug monitoring being used in conjunction with the twice-daily amikacin regimen, and it is not a common practice for medications with a narrow therapeutic drug index, such as amikacin. The current study aimed to determine whether patients using the standard weight-based regimen achieved therapeutic levels of amikacin, and to evaluate the safety and effectiveness of the amikacin dosage regimen in the treatment of urinary tract infections (UTIs).

Materials & Methods: In this prospective observational study, patients of both sexes who were hospitalized with a diagnosis of UTI and treated with intravenous amikacin for at least seven days, either with or without additional antibiotics, were selected from the inpatient department of the Rizgary Teaching Hospital. A total of 210 participants were enrolled in this study by convenience sampling method.

Results: Of the participants, 42.9% were male. The mean daily Amikacin was 548.6±97.3 mg. Steady-state maximum (Cssmax) and minimum (Cssmin) concentrations were 27.6±4.6 mg/L and 4.4±1.6 mg/L, respectively.

Conclusion: The present study demonstrated clear associations between higher trough concentrations and increased risks of ototoxicity and nephrotoxicity, with CssMin ≥4 mg/L representing a critical toxicity threshold. In contrast, achieving higher peak levels (CssMax ≥30 mg/L) improved clinical cure rates.

KEY WORDS: Amikacin; Pharmacokinetics; Safety; Urinary tract infections.

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INTRODUCTION

Aminoglycosides (AG) have a narrow therapeutic index; therefore, their dose range is small. A well-established concentration-effect relationship (toxicity) and medication monitoring are indicated for all aminoglycoside users. Amikacin, gentamicin, tobramycin, kanamycin, and streptomycin are antimicrobials in this class.[1] In concentration-dependent killing, aminoglycosides kill bacteria by reaching high binding-site concentrations. The strongest responses occurred at a ratio of peak concentration (Cmax) to the minimum inhibitory concentration (MIC) between 8 and 10. Stated differently, peak plasma concentrations have to be at least 8 or 10 times the suspected bacteria's MIC.[2] Due to the risk of ototoxicity and nephrotoxicity, AGs are often not used as the first treatment for susceptible species. Aminoglycosides can cause acute kidney injury (AKI) in approximately 5–25% of treatment protocols.[3] Aminoglycosides have also been linked to vestibular and cochlear toxicity, which causes disequilibrium and hearing loss, respectively.[1] Amikacin is a semisynthetic antibiotic that belongs to the class of drugs known as aminoglycosides. It is often used to treat infections caused by gram-negative bacteria, including urinary tract infections (UTI), sepsis, and tuberculosis, which are resistant to several drugs. It prevents the synthesis of proteins and kills

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vulnerable organisms in a concentration-dependent manner. Its therapeutic index is extremely narrow, and it has a post-antibiotic action. It may result in permanent ototoxicity and reversible nephrotoxicity.[4] Serum creatinine levels are monitored to assess amikacin-related nephrotoxicity, whereas ototoxicity often goes undetected until the patient experiences permanent hearing loss. Therapeutic drug monitoring (TDM) is recommended for medications with narrow therapeutic indices. However, TDM of amikacin is infrequently performed. Limited data exists on TDM for the twice-daily amikacin regimen. Variations in amikacin blood concentrations are influenced by factors such as body weight and clinical conditions, including burn injuries and sepsis, both intraindividually and interindividually.[5] If blood drug levels rise, this may reduce the medication's efficacy and cause toxicity. This may have caused amikacin resistance. The antibiotic dose is important and TDM may assist in the early detection of amikacin toxicity. Namazi et al. found that only 48% of the patients followed amikacin monotherapy recommendations. Patients taking amikacin need close TDM.[6] Streetman et al. observed that individual amikacin monitoring reduced side effects and therapeutic costs.[7] Only a limited number of studies have evaluated the function of TDM of amikacin or investigated the correlation between blood drug levels and clinical outcomes as well as their adverse effects.[8] The current study aimed to ascertain whether the standard weight-based dosage of amikacin results in therapeutic levels in patients with UTIs, and to assess the safety and efficacy of this dosing regimen in managing UTIs.

MATERIAL AND METHODS

Study Design: This prospective observational study was conducted at the Rizgary Teaching Hospital between July and December 2023. The study participants were chosen from the inpatient urology department of the Rizgary Teaching Hospital. This study was approved by the Kurdistan Higher Council of Medical Specialty's Ethical Committee. This study was conducted according to the principles outlined in the Declaration of Helsinki and the Good Clinical Practice criteria set by the International Conference on Harmonization.

Patient Population and Criteria: Participants of both sexes were enrolled in the inpatient department of Rizgary Teaching Hospital. Treatment involved the administration of intravenous amikacin, either alone or in combination with other antibiotics, for a minimum duration of 7 days. Patients receiving concurrent nephrotoxic or ototoxic medications, such as amphotericin B or vancomycin; those with a history of chronic suppurative otitis media, congenital deafness, or any auditory problems; pregnant or lactating women; those undergoing immunosuppressive therapy; those with HIV infection/AIDS; and those with renal impairment were excluded from the study.

Sampling Method and Sample Size: The sample size for this study was calculated based on the primary outcome measures, which included the incidence of ototoxicity and nephrotoxicity associated with amikacin treatment in patients with UTI.

$$n = \frac{z^2 \times p \times (1-p)}{d^2}$$

Where n=required sample size, Z=Z-value (the number of standard deviations from the mean, corresponding to the desired confidence level; for a 95% confidence level, Z=1.96), P= estimated proportion of the population with the characteristic of interest (incidence of ototoxicity or nephrotoxicity), and d=margin of error (0.05). Based on prior studies and clinical observations, the mean incidence of nephrotoxicity with amikacin was estimated to be around 15%.[1]

$$n = \frac{(1.96)^2 \times 0.15 \times (1-0.15)}{(0.05)^2} \approx 196$$

The sample size for this study was initially calculated as 196 participants. However, to further enhance the precision and robustness of the study results, 210 individuals were included in this study based on the convenience sampling method.

Study Procedure: Demographic data (age, sex, height, weight, and drug use) and clinical evaluation details were collected from the case files and interviews. Urine cultures and serum creatinine levels were obtained shortly after admission. Serum creatinine levels were measured every three days. Pure tone audiometry (250-8000 Hz) was conducted within 24 hours. Patients received 7.5 mg/kg amikacin intravenously twice daily for 30 minutes. Blood samples (3 mL) were drawn before the third dose to measure trough concentration (Ctrough) and 30 min post-infusion to determine maximum concentration (Cmax).[9] For five minutes, the blood samples were centrifuged at 2500 rpm. Plasma was extracted and stored at 28°C for analysis using liquid chromatography-tandem mass spectrometry (Waters, Milford). Daily evaluations of symptom remission (fever, hearing abnormalities, vertigo, tinnitus, ataxia, nystagmus, fullness, headache, nausea, and vomiting) were conducted. Serum creatinine concentrations were determined using Jaffe's technique.[10] By using a Beckman Coulter multi-analyzer (Beckman Coulter chemical analyzer AU680 from Tokyo, Japan), the necessary adjustments were made. Creatinine clearance was estimated using the modified Cockcroft-Gault method. Nephrotoxicity diagnosis was based on an increase in baseline blood creatinine of 0.5 mg/dL or 50%.[11] Patients were categorized into two groups based on amikacin Ctrough concentrations (threshold: 4 mg/L).[12] The relationship between Ctrough and serum creatinine or creatinine clearance was evaluated three times over seven days.

Statistical analysis: Data were presented as the mean ± standard deviation for continuous data or as counts and percentages for categorical variables. Comparisons of continuous variables between pre- and post-treatment were performed using paired t-tests or Wilcoxon signed-rank tests after checking for normality using the Shapiro-Wilk test. Categorical variables were compared using the McNemar's test. Comparisons of the composite endpoints between groups were performed using the Wilcoxon rank sum test. All tests were two-sided, and a p-value less than 0.05 was deemed to be statistically significant. The composite endpoint for treatment efficacy was defined as the sum of all UTI symptoms after treatment. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient selection and baseline characteristics

Figure 1 shows the flowchart of the present study. The mean age was 33.7±9.4 years, and the mean weight was 73.2±13.0 kg. Of the participants, 42.9% were male. The mean daily dose of Amikacin was 548.6±97.3 mg. Steady-state maximum (Cssmax) and minimum (Cssmin) concentrations were 27.6±4.6 mg/L and 4.4±1.6 mg/L, respectively (Table 1).

Table 1: The research group's baseline clinical and demographic parameters (N=210)

Characteristic	N = 210*
Age (years)	33.7±9.4
Weight (kg)	73.2±13.0
Height (m)	167.0±9.5
Gender	90 (42.9%)
Amikacin daily dose (mg)	548.6±97.3
Cssmax (mg/L)	27.6±4.6
Cssmin (mg/L)	4.4±1.6

*Mean±SD; n (%)

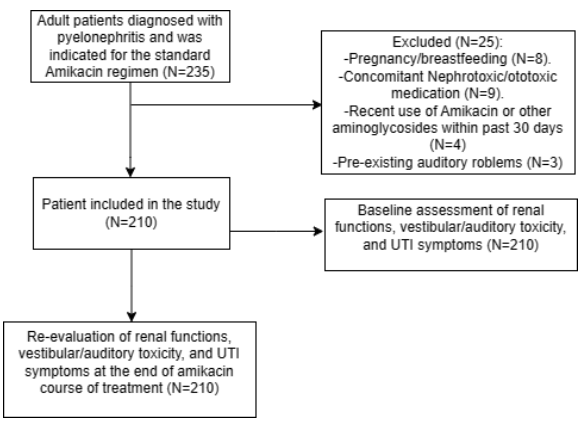

Figure 1: Study flowchart.

Association between amikacin trough levels at steady state and ototoxicity: For patients with Css-Min <4 mg/L, there were no significant changes in the incidence of most ototoxicity symptoms post-treatment, including equilibrium, hearing abnormalities, tinnitus, ataxia, nystagmus, and fullness (p>0.05). Nevertheless, there was a substantial decrease in the occurrence of nausea and vomiting (both p <0.001). Conversely, in patients with CssMin ≥4 mg/L, a significant increase in the incidence of equilibrium (from 0.8% to 17.6%, p <0.001), hearing abnormalities (from 0.0% to 10.4%, p <0.001), vertigo (from 2.4% to 18.4%, p<0.001), tinnitus (from 0.0% to 6.4%, p = 0.013), ataxia (from 1.6% to 13.6%, p=0.001), and headache (from 3.2% to 39.2%, p<0.001) was observed. Increases in nausea and vomiting were also significant in this group (from 41.6% to 84.0% and 26.4% to 81.6%, respectively; both p<0.001). The composite endpoint of ototoxicity was significantly higher in patients with CssMin≥4 mg/L than in those with CssMin<4 mg/L (mean 0.1±0.5, 2.8±1.7, p<0.001) (Table 2, Figure 2).

Association between amikacin trough levels at steady state and nephrotoxicity: For patients with CssMin <4 mg/L, the mean serum creatinine (SCR) levels slightly decreased from 0.9±0.3 mg/dL to 0.8±0.1 mg/dL post-treatment, though this change was not statistically significant (p=0.11). Creatinine clearance showed a significant improvement from 106.2±20.9 ml/min to 113.4±13.9 ml/min (p=0.001). Conversely, in the group with CssMin ≥4 mg/L, SCR levels significantly increased from 0.8±0.3 mg/dL to 1.4±0.5 mg/dL (p<0.001), and creatinine clearance notably decreased from 106.5±21.6 ml/min to 78.7±29.1 ml/min (p < 0.001). The incidence of nephrotoxicity was significantly higher in patients with trough levels of ≥4 mg/L (14.1% vs. 56.0%, p<0.001), suggesting a strong association between higher trough levels of amikacin and nephrotoxicity (Table 3).

Association between amikacin maximum concentrations at steady state with infection resolution: In the group with CssMax < 30 mg/L, there was a notable reduction in fever (from 68.5% to 10.1%, p < 0.001), urgency (from 78.5% to 21.5%, p < 0.001), frequency (from 88.6% to 20.8%, P < 0.001), pyuria (from 70.5% to 14.1%, P < 0.001), and dysuria (from 56.4% to 12.1%, P < 0.001) after completion of amikacin treatment. Similarly, in the group with CssMax ≥ 30 mg/L, there were marked decreases in the incidence of fever (from 67.2% to 1.6%, p < 0.001), urgency (from 73.8% to 0.0%, p < 0.001), frequency (from 77.0% to 3.3%, p < 0.001), pyuria (from 78.7% to 0.0%, p < 0.001), and dysuria (from 65.6% to 1.6%, p < 0.001). The composite endpoint of efficacy, which combined these UTI symptoms, showed a significantly higher magnitude of improvement post-treatment in patients with CssMax ≥ 30mg/L compared to those with CssMax < 30 mg/L (0.8±1.5 vs. 0.1±0.2, p < 0.001) (Table 4, Figure 3).

Table 2: Comparing the incidence of different signs/symptoms of ototoxicity before and after the end of amikacin courses stratified by steady-state trough levels (N=210)

	CssMin<4 mg/L			CssMin≥4 mg/L		
Characteristic	Before, N=85[1]	After, N=85[1]	p-value[2]	Before, N=125[1]	After, N=125[1]	p-value[2]
Equilibrium	0 (0.0%)	0 (0.0%)	NA[3]	1 (0.8%)	22 (17.6%)	<0.001
Hearing Abnormality	0 (0.0%)	0 (0.0%)	NA[3]	0 (0.0%)	13 (10.4%)	<0.001
Vertigo	2 (2.4%)	0 (0.0%)	0.48	3 (2.4%)	23 (18.4%)	<0.001
Tinnitus	1 (1.2%)	0 (0.0%)	>0.99	0 (0.0%)	8 (6.4%)	0.013
Ataxia	0 (0.0%)	0 (0.0%)	NA[3]	2 (1.6%)	17 (13.6%)	0.001
Nystagmus	0 (0.0%)	0 (0.0%)	NA[3]	0 (0.0%)	4 (3.2%)	0.13
Fullness	0 (0.0%)	1 (1.2%)	>0.99	1 (0.8%)	5 (4.0%)	0.2
Headache	6 (7.1%)	1 (1.2%)	0.13	4 (3.2%)	49 (39.2%)	<0.001
Nausea	30 (35.3%)	5 (5.9%)	<0.001	52 (41.6%)	105 (84.0%)	<0.001
Vomiting	27 (31.8%)	4 (4.7%)	<0.001	33 (26.4%)	102 (81.6%)	<0.001
Composite endpoint of ototoxicity	0.1±0.5			2.8±1.7		<0.001

[1]n (%); [2]McNemar's chi-squared test with continuity correction; [3]P-value cannot be estimated owing to zero counts before and after treatment.

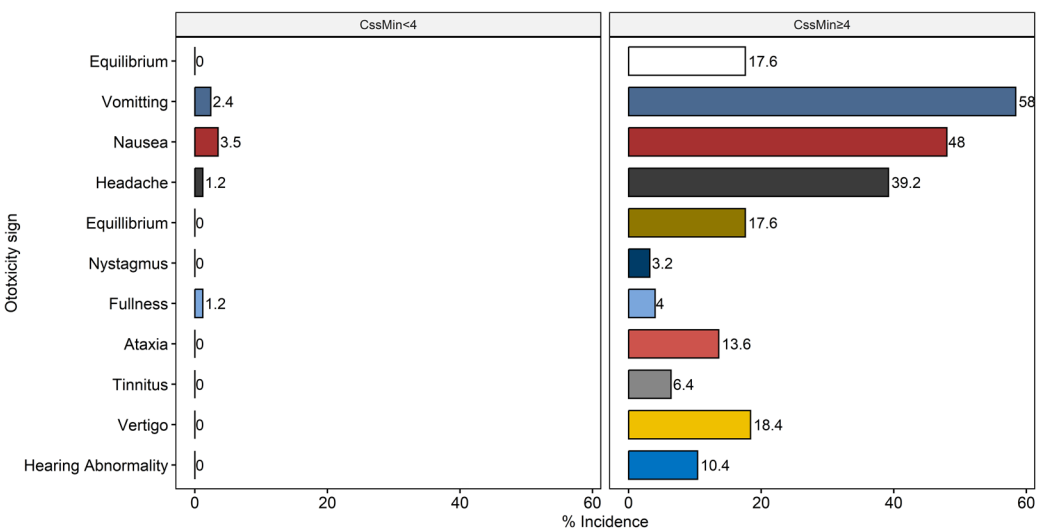

Figure 2: Comparison of the incidence of new-onset signs and symptoms of amikacin-related ototoxicity stratified based on steady-state amikacin trough levels.

Table 3: Comparing the incidence of different signs/symptoms of nephrotoxicity before and after the end of amikacin courses stratified by steady-state trough levels (N=210)

	CssMin<4 mg/L			CssMin≥4 mg/L		
Characteristic	Before, N=85[1]	After, N=85[1]	p-value[2]	Before, N=125[1]	After, N=125[1]	p-value[2]
SCR (mg/dL)	0.9±0.3	0.8±0.1	0.11	0.8±0.3	1.4±0.5	<0.001
Creatinine clearance (ml/min)	106.2±20.9	113.4±13.9	0.001	106.5±21.6	78.7±29.1	<0.001
Nephrotoxicity	12 (14.1%)			70 (56.0%)		<0.001

[1]Mean±SD; n (%); [2]Wilcoxon signed rank test with continuity correction; McNemar's Chi-squared test

Table 4: Evaluation of clinical resolution of different UTI signs/symptoms at the end of amikacin courses stratified by steady-state maximum concentrations (N=210)

	CssMin<4 mg/L			CssMin≥4 mg/L		
Characteristic	Before, N=149[1]	After, N=149[1]	p-value[2]	Before, N=61[1]	After, N=61[1]	p-value[2]
Fever	102 (68.5%)	15 (10.1%)	<0.001	41 (67.2%)	1 (1.6%)	<0.001
Urgency	117 (78.5%)	32 (21.5%)	<0.001	45 (73.8%)	0 (0.0%)	<0.001
Frequency	132 (88.6%)	31 (20.8%)	<0.001	47 (77.0%)	2 (3.3%)	<0.001
Pyuria	105 (70.5%)	21 (14.1%)	<0.001	48 (78.7%)	0 (0.0%)	<0.001
Dysuria	84 (56.4%)	18 (12.1%)	<0.001	40 (65.6%)	1 (1.6%)	<0.001
Composite endpoint of efficacy	0.8±1.5			0.1±0.2		<0.001

[1]n (%); [2]McNemar's Chi-squared test with continuity correction

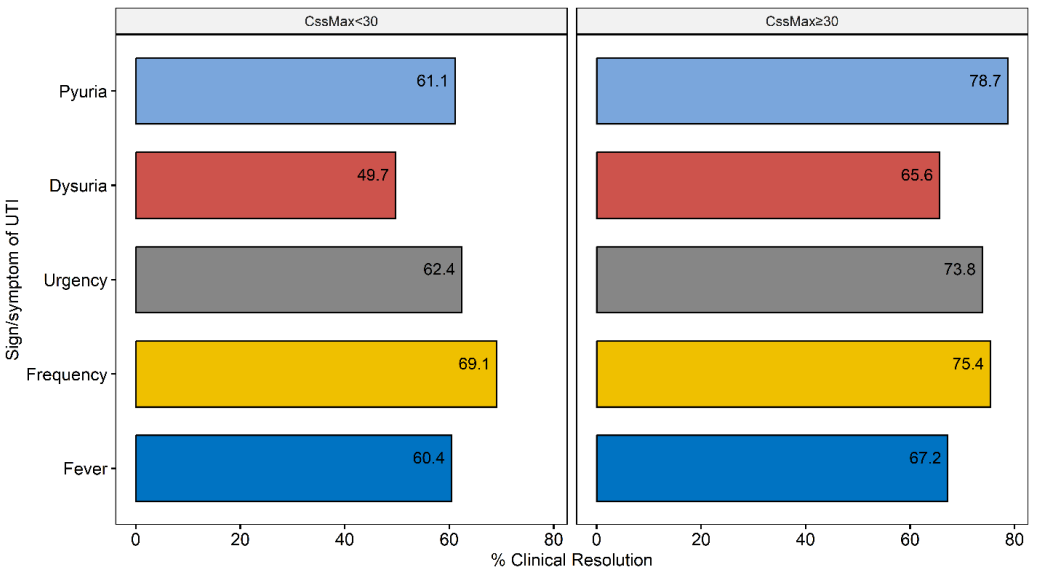

Figure 3: Comparison of the rates of clinical resolution of different UTI signs/symptoms at the end of the 7-day amikacin therapy stratified based on steady-state trough levels.

DISCUSSION

The present study evaluated the safety, efficacy, and pharmacokinetics of a standard weight-based dosing regimen of amikacin in UTI patients. These findings indicated that while the dosing regimen achieved therapeutic levels, it was associated with a significant risk of ototoxicity and nephrotoxicity in patients with higher steady-state trough concentrations (CssMin ≥ 4 mg/L). Conversely, those with CssMin < 4 mg/L demonstrated a more favorable safety profile, with significant reductions in nephrotoxicity and ototoxicity. Notably, higher steady-state peak concentrations (CssMax ≥ 30 mg/L) were associated with enhanced clinical resolution of UTI symptoms, underscoring the importance of optimizing dosing strategies to balance the therapeutic efficacy and safety.

This study found a significant increase in ototoxicity symptoms in patients with CssMin levels ≥ 4 mg/L. This result corroborates findings from previous studies that have highlighted the ototoxic potential of aminoglycosides.[13] Rivetti et al. (2023), showed that maintaining lower trough levels of aminoglycosides could mitigate the risk of ototoxicity without compromising therapeutic efficacy.[13] The present study reinforces these findings, indicating that maintaining CssMin < 4 mg/L is crucial for minimizing ototoxic side effects. However, it is essential to balance these lower levels with the need for adequate drug exposure to ensure efficacy, as overly aggressive reductions could lead to treatment failures. [14] In contrast, a study by Endo et al. (2022),[15] showed that ototoxicity was more likely to occur at low doses (≥10 µg/mL). Additionally, despite the agreement with the association between trough levels and the incidence of cytotoxicity, the current study findings contradict the significantly higher reported rate of amikacin-induced hearing loss with amikacin in a recent study by Wrohan et al. (2021). This could be emphasized by the fact that multidrug-resistant TB (MDR-TB) patients received

significantly higher doses of amikacin; Also, the use of objective audiometric assessment in the majority of the studies in this meta-analysis, unlike the present study, which implemented subjective assessment of self-reported hearing abnormalities only.[16]

Nephrotoxicity was observed in of 39%, with an extremely high incidence in patients with steady-state trough levels ≥ 4 mg/L. The amount of nephrotoxicity observed in the present study was higher than that reported in the study by Kim et al. (2019).[17] The varying rates of amikacin-induced nephrotoxicity may be related to the correlation between nephrotoxicity of aminoglycosides and factors such as dosage,[18] length of therapy,[19] and concurrent use of other antimicrobials.[20] The current study provides evidence linking higher amikacin trough concentrations to increased nephrotoxicity risk, with over half of patients experiencing toxicity at CssMin ≥4 mg/L. A recent study suggested that Cmin <10 mg/L was associated with a considerably decreased occurrence rate of nephrotoxicity than Cmin ≥10 mg/L.[9] In line with the present findings, several other studies suggested the association between both nephrotoxicity and ototoxicity with trough levels >4 mg/L.[21]

While avoiding toxicity is imperative, underdosing aminoglycosides raises concerns for treatment failure and antibiotic resistance. The current study showed that peak amikacin concentrations ≥30 mg/L resulted in better clinical cure of urinary tract infection, with greater resolution of symptoms, including fever, urgency, frequency, pyuria, and dysuria. The concentration-dependent killing of aminoglycosides likely explains the improved efficacy of higher CssMax values. Prior pharmacokinetic-pharmacodynamic (PK-PD) studies have suggested that peak levels of 8-10 times the MIC are required for bactericidal activity against gram-negative.[22] This is consistent with the results of a recent systematic review by Goodlet et al. (2019).[23] Additionally, a retrospective study was conducted to examine the effectiveness of amikacin in treating UTIs caused by extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli (Ec) and Klebsiella pneumoniae (Kp). The results showed a clinical success rate of 97.2%, with bacteriological success rates of 91.7% on the third day of therapy, 97.1% at the conclusion of treatment, and 94.1% 7–10 days after treatment. A follow-up period of 28–32 days after treatment showed a 12% reinfection rate, with no relapses identified.[24] It should be noted that the slightly higher cure rate observed in this study could be related to different infection types (cystitis) and the administered amikacin dosing compared to the current study.

Limitations and Future Directions: The present study had several limitations. The restricted inclusion of adult patients with UTIs from a single center may restrict the generalizability of the findings. As this was not a randomized controlled trial, it was subject to possible confounding factors and bias. The short follow-up period precluded the assessment of long-term ototoxicity and nephrotoxicity arising from amikacin therapy. Serial audiometric testing would allow for a more rigorous quantification of hearing loss. The measurement of amikacin levels was also limited to peak and trough concentrations at steady state, rather than intensive pharmacokinetic sampling to fully characterize exposure. Future studies should include larger multicenter trials, blinded treatment allocation, serial ototoxicity monitoring, and intensive pharmacokinetic sampling will be important to validate the defined exposure targets for toxicity and efficacy.

CONCLUSION

In conclusion, this study emphasizes the importance of maintaining an appropriate amikacin trough and peak levels to balance adverse events and therapeutic efficacy in UTI management. Higher trough concentrations (CssMin ≥4 mg/L) are linked to increased ototoxicity and nephrotoxicity, whereas higher peak levels (CssMax ≥30 mg/L) improve clinical cure rates. These findings underscore the utility of monitoring to maximize bacterial killing and minimize toxicity, thereby guiding precision dosing in adult UTI treatment.

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CONFLICT OF INTEREST
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AUTHORS' CONTRIBUTION

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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.