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OPTIMIZING AMINOGLYCOSIDE DOSING IN CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE PATIENTS UNDERGOING INTERMITTENT HEMODIALYSIS: CARDIOVASCULAR IMPLICATIONS AND CLINICAL OUTCOMES

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Introduction: Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) undergoing intermittent hemodialysis frequently require aminoglycoside therapy for severe bacterial infections. Altered pharmacokinetics in renal dysfunction increase the risk of drug accumulation, nephrotoxicity, ototoxicity and cardiovascular complications associated with electrolyte imbalance, volume overload, systemic infection. Optimizing aminoglycoside dosing is therefore essential to improve both renal and cardiovascular outcomes.

Methodology:A cross-sectional study was conducted among 220 adult CKD and ESRD patients receiving intermittent hemodialysis who were prescribed aminoglycosides at tertiary care hospital. Demographic characteristics, comorbidities, dialysis-related factors, aminoglycoside dosing regimens, therapeutic drug monitoring, renal function parameters, cardiovascular status and clinical outcomes were recorded using a structured data collection form. Descriptive statistics and multivariable logistic regression were used to identify factors associated with favorable clinical outcomes, with statistical significance set at $p < 0.05$.

Results: The mean age of participants was 58.7 ± 13.2 years, and 61.8% were male. Therapeutic drug monitoring-guided dosing was implemented in 54.5% of patients and was associated with significantly higher treatment success (82.5% vs. 67.3%, $p = 0.003$), lower aminoglycoside-associated toxicity (11.7% vs. 25.8%, $p = 0.009$) and fewer cardiovascular complications including arrhythmias, intradialytic hypotension and heart failure exacerbations (18.3% vs. 31.4%, $p = 0.018$). Independent predictors of favorable outcomes included individualized dosing according to dialysis schedule (adjusted OR = 2.41, 95% CI: 1.35–4.29), therapeutic drug monitoring (adjusted OR =

2.76, 95% CI: 1.52–5.02) and preserved residual renal function (adjusted OR = 1.89, 95% CI: 1.08–3.30).

Conclusion: Individualized aminoglycoside dosing strategies based on renal function, dialysis timing and therapeutic drug monitoring were associated with improved treatment efficacy, reduced nephrotoxicity and cardiovascular complications in CKD and ESRD patients undergoing intermittent hemodialysis. Incorporating a multidisciplinary cardio renal approach may further optimize antimicrobial therapy and improve clinical outcomes in this high-risk population.

Keywords: Chronic kidney disease (CKD), End-stage renal disease (ESRD), Intermittent hemodialysis, Aminoglycosides, Therapeutic drug monitoring, Individualized dosing, Nephrotoxicity, Cardiovascular complications,

INTRODUCTION:

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) represent major global public health challenges, affecting approximately 10–15% of the adult population worldwide[1,2]. Progressive deterioration of renal function results in impaired clearance of endogenous metabolites and numerous medications, thereby increasing the risk of drug accumulation, adverse drug reactions and poor clinical outcomes. Patients with advanced CKD frequently require intermittent hemodialysis for maintenance of fluid, electrolyte and metabolic homeostasis[3-6]. Despite improvements in dialysis techniques, infectious complications remain one of the leading causes of hospitalization and mortality among these patients.

Aminoglycosides, including gentamicin, amikacin and tobramycin are important antimicrobial agents for the treatment of severe Gram-negative bacterial infections, infective endocarditis, catheter-related bloodstream infections, urinary tract infections and hospital-acquired pneumonia [7-9]. These antibiotics exhibit concentration-dependent bactericidal activity and a prolonged post-antibiotic effect making them valuable agents in critically ill patients[10]. However, aminoglycosides possess a narrow therapeutic index and their elimination occurs almost exclusively through glomerular filtration. Consequently, patients with impaired renal function are highly susceptible to drug accumulation, nephrotoxicity, vestibular toxicity and irreversible ototoxicity[11].

Intermittent hemodialysis significantly alters aminoglycoside pharmacokinetics. Drug removal depends upon molecular weight, protein binding, dialysis membrane characteristics, dialysis duration, blood flow rate and residual renal function[12,13]. Conventional dosing regimens developed for individuals with normal renal function frequently result in either subtherapeutic concentrations leading to treatment failure or excessive drug exposure causing toxicity in dialysis patients [14-16]. Therefore, individualized dosing based on renal function and dialysis schedule has become increasingly important.

Therapeutic drug monitoring (TDM) has emerged as an effective strategy to optimize aminoglycoside therapy by maintaining therapeutic peak concentrations while minimizing toxic trough levels[17]. Evidence suggested that individualized dosing combined with serum drug concentration monitoring improves antimicrobial efficacy and reduces adverse events. Nevertheless, TDM remains underutilized in many healthcare settings due to limited laboratory resources and variability in institutional protocols [18-20].

Beyond nephrotoxicity, cardiovascular complications have gained increasing attention in CKD and ESRD patients receiving aminoglycosides. Electrolyte disturbances, fluid overload, chronic inflammation and systemic infections contribute substantially to arrhythmias, intradialytic hypotension, heart failure exacerbations and cardiovascular mortality [21,22]. Appropriate antimicrobial therapy leading to rapid infection control may indirectly reduce cardiovascular stress and improve hemodynamic stability. Conversely, inappropriate dosing may prolong infection, increase systemic inflammation and worsen cardiovascular outcomes [23].

Despite growing recognition of individualized antimicrobial therapy, limited evidence is available regarding the combined effects of aminoglycoside dosing optimization on both infectious and

cardiovascular outcomes among patients undergoing intermittent hemodialysis. Therefore, this study aimed to evaluate dosing practices, therapeutic drug monitoring, treatment efficacy, drug-related toxicity and cardiovascular outcomes in CKD and ESRD patients receiving aminoglycosides during intermittent hemodialysis.

OBJECTIVES

The objective of this study is to evaluate the effectiveness of optimized aminoglycoside dosing strategies in patients with chronic kidney disease and end-stage renal disease undergoing intermittent hemodialysis, assess their impact on cardiovascular complications and overall clinical outcomes. Specifically, the study aim to evaluate prescribing patterns therapeutic drug monitoring practices, and treatment success along with aminoglycoside-associated adverse effects.

METHODOLOGY

This was a hospital-based analytical cross-sectional study conducted over a period of 12 months in the tertiary care nephrology and dialysis units in Dow university Hospital. The study population included 220 adult patients with CKD receiving intermittent hemodialysis who were prescribed aminoglycosides for documented bacterial infections. Patients were enrolled using consecutive sampling. Data collection included demographic characteristics, duration of CKD, dialysis frequency, residual renal function, type of infection, aminoglycoside prescribed, dosing regimen, timing of administration, therapeutic drug monitoring, laboratory parameters, echocardiographic findings, cardiovascular complications, treatment response, hospital stay duration and drug toxicity.

Ethical considerations

The study was approved by the institutional IRB of Dow university of Heath sciences

STATISTICAL ANALYSIS

For statistical analysis, data were entered and analyzed using IBM SPSS version 22. Continuous variables were expressed as Mean ± SD and categorical variables as frequency and percentage. The Chi-square test was used to compare categorical variables and multivariable logistic regression was performed to identify predictors of favorable clinical outcomes. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 220 adult patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) receiving intermittent hemodialysis and prescribed aminoglycoside therapy were included in the study. The results describe the demographic characteristics, renal function parameters, aminoglycoside utilization patterns, cardiovascular characteristics, treatment outcomes and predictors of favorable cardiorenal outcomes.

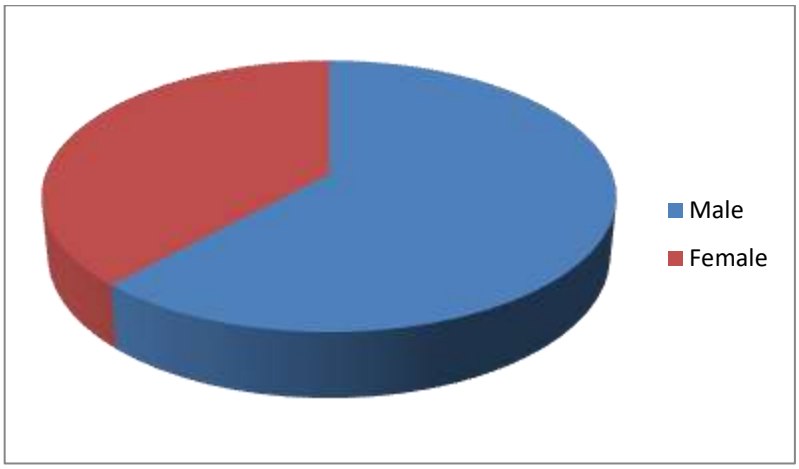


Figure 1 showed the Gender distribution of the participants

The study population had a mean age of 58.7 ± 13.2 years, with more than half (50.9%) belonging to the 50–69-year age group. Males accounted for 61.8% of participants. Hypertension (82.7%) and diabetes mellitus (58.2%) were the predominant comorbidities, reflecting the major etiological factors responsible for CKD and ESRD

Table 1 showed the Age distribution of the participants(n = 220)

Variable	Frequency (%)
Age <50 years	48 (21.8)
Age 50–69 years	112 (50.9)
Age ≥70 years	60 (27.3)

Approximately one-third (34.5%) had heart failure, emphasizing the high cardiovascular burden in dialysis patients. Residual renal function was preserved in 44.5% of patients, an important factor influencing aminoglycoside pharmacokinetics and overall prognosis.

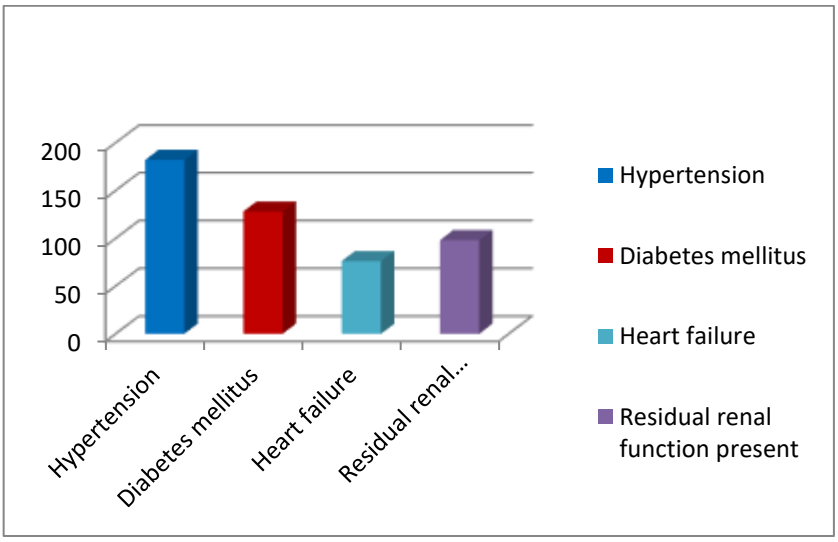


Figure 2 showed co-morbids as an etiological factors for CKD

Renal assessment demonstrated severe kidney dysfunction among the study population. Half of the participants (50.0%) had ESRD requiring maintenance hemodialysis. Mean serum creatinine (7.8 ± 2.6 mg/dL) and blood urea nitrogen (86.4 ± 24.8 mg/dL) were markedly elevated, while mean eGFR **(**11.3 ± 5.4 mL/min/1.73 m²**)** confirmed advanced renal impairment.

Table 2. Baseline Renal Characteristics and Laboratory Parameters (n = 220)

Variable	Frequency (%) / Mean ± SD
Serum creatinine (mg/dL)	7.8 ± 2.6
Blood urea nitrogen (mg/dL)	86.4 ± 24.8
eGFR (mL/min/1.73m²)	11.3 ± 5.4
Serum potassium (mmol/L)	5.6 ± 0.8
Serum sodium (mmol/L)	135.8 ± 4.6
Residual urine output >500 mL/day	98 (44.5)
Dialysis three times/week	136 (61.8)

Hyperkalemia was common, with a mean serum potassium level of 5.6 ± 0.8 mmol/L. Residual urine output was preserved in 44.5%**,** which may contribute to better drug clearance and improved outcomes.

Table 3. Aminoglycoside Utilization Pattern (n = 220)

Variable	Frequency (%)
Gentamicin	104 (47.3)
Amikacin	82 (37.3)
Tobramycin	34 (15.4)
Post-dialysis dosing	146 (66.4)
Individualized dosing	132 (60.0)
Therapeutic drug monitoring (TDM)	120 (54.5)

Gentamicin was the most commonly prescribed aminoglycoside (47.3%), followed by amikacin (37.3%) and tobramycin (15.4%). Approximately two-thirds (66.4%) received aminoglycosides immediately after dialysis sessions, while individualized dosing protocols were used in **60.0%** of patients. Therapeutic drug monitoring was performed in 54.5%**,** demonstrating increasing implementation of precision dosing practices.

Table 4. Renal Outcomes According to Therapeutic Drug Monitoring

Outcome	TDM (n=120)	No TDM (n=100)	p-value
Nephrotoxicity	14 (11.7%)	26 (26.0%)	0.009
Increase in serum creatinine >0.5 mg/dL	18 (15.0%)	34 (34.0%)	0.002
Dialysis frequency increased	10 (8.3%)	22 (22.0%)	0.006
Residual renal function preserved	69 (57.5%)	29 (29.0%)	<0.001

Therapeutic drug monitoring significantly improved renal safety outcomes. Nephrotoxicity occurred in only 11.7% of patients receiving TDM compared with 26.0% in those without monitoring ($p = 0.009$). Similarly, significant rises in serum creatinine and increased dialysis requirements were less frequent among monitored patients. Preservation of residual renal function was nearly twice as common in the TDM group (57.5% vs. 29.0%; $p < 0.001$), indicating the effectiveness of individualized dosing strategies.

Table 5. Baseline Cardiovascular Clinical Characteristics (n = 220)

Variable	Frequency (%) / Mean ± SD
Hypertension	182 (82.7)
Heart failure	76 (34.5)
Coronary artery disease	54 (24.5)
Elevated Troponin-I	37 (16.8)
Elevated NT-proBNP	81 (36.8)

Cardiovascular disease was highly prevalent in the study. Hypertension affected 82.7% of patients, while 34.5% had heart failure and 24.5% had coronary artery disease. Elevated cardiac biomarkers further reflected the high burden of cardiovascular disease among dialysis patients.

Table 6. Cardiovascular Outcomes According to Therapeutic Drug Monitoring

Outcome	TDM (%)	No TDM (%)	p-value
Arrhythmias	13.3	23.0	0.041
Intradialytic hypotension	15.8	29.0	0.018
Heart failure exacerbation	10.8	18.0	0.047
Elevated Troponin-I	11.7	22.0	0.029
Cardiovascular hospitalization	8.3	17.0	0.035
Composite cardiovascular complications	18.3	31.4	0.018

Patients managed with therapeutic drug monitoring experienced significantly fewer cardiovascular complications than those receiving conventional dosing. The incidence of arrhythmias, intradialytic hypotension, heart failure exacerbations, elevated troponin-I levels, and cardiovascular-related hospitalizations was significantly reduced. Overall, optimized aminoglycoside dosing reduced composite cardiovascular complications from 31.4% **to** 18.3%, highlighting the clinical benefits of individualized pharmacokinetic monitoring.

Table 7. Therapeutic Drug Monitoring and Clinical Outcomes

Outcome	TDM (%)	No TDM (%)	p-value
Treatment success	82.5	67.3	0.003
Nephrotoxicity	11.7	25.8	0.009
Cardiovascular complications	18.3	31.4	0.018

Patients undergoing therapeutic drug monitoring experienced significantly better treatment outcomes. Treatment success was higher among the TDM group (82.5% vs. 67.3%**,** p = 0.003). Similarly, nephrotoxicity (11.7% vs. 25.8%**)** and cardiovascular complications (18.3% vs. 31.4%) were significantly reduced. These findings support routine implementation of TDM in dialysis patients receiving aminoglycosides.

Table 8. Predictors of Favorable Cardiorenal Outcomes (Multivariable Logistic Regression)

Variable	Adjusted OR	95% CI	p-value
Therapeutic drug monitoring	2.91	1.62–5.34	<0.001
Individualized post-dialysis dosing	2.46	1.36–4.38	0.003
Preserved residual renal function	2.08	1.19–3.69	0.011
Controlled systolic BP (<140 mmHg)	1.94	1.12–3.41	0.022
LVEF ≥50%	2.12	1.21–3.84	0.016
Diabetes mellitus	0.66	0.39–0.96	0.031
Heart failure	0.59	0.34–0.93	0.028
Age ≥70 years	0.61	0.37–0.95	0.039

Multivariable logistic regression identified therapeutic drug monitoring as the strongest independent predictor of favorable cardiorenal outcomes, increasing the likelihood of successful treatment by nearly threefold. Individualized post-dialysis dosing, preserved residual renal function, controlled systolic blood pressure, and preserved left ventricular ejection fraction also independently improved clinical outcomes. Conversely, diabetes mellitus, heart failure, and advanced age significantly reduced the probability of favorable outcomes, emphasizing the importance of individualized antimicrobial therapy and comprehensive cardiorenal management in this high-risk population.

DISCUSSION

Chronic kidney disease and end-stage renal disease are major health problems with high morbidity and mortality especially in patients on maintenance hemodialysis who are also at increased risk for severe bacterial infections due to immune dysfunction, frequent vascular access, repeated hospitalizations and multiple comorbidities[24,25]. Aminoglycosides remain important broad-spectrum antibiotics for serious Gram-negative infections, but their use in CKD and ESRD is challenging because of altered pharmacokinetics from reduced renal clearance[26]. Improper dosing can cause drug accumulation, nephrotoxicity, ototoxicity, electrolyte disturbances and cardiovascular instability while under-dosing may lead to treatment failure and antimicrobial resistance. Therefore individualized dosing based on renal function, dialysis timing and therapeutic drug monitoring is essential to balance efficacy and safety. In addition, optimized aminoglycoside therapy may also have cardiovascular benefits since CKD and ESRD patients frequently suffer from hypertension, diabetes,

heart failure and atherosclerosis that predispose them to adverse cardiac events[27]. By minimizing nephrotoxicity, maintaining electrolyte balance and reducing systemic inflammation, appropriate antimicrobial dosing may improve cardiovascular stability and overall outcomes. This study evaluated individualized aminoglycoside dosing strategies in CKD and ESRD patients undergoing intermittent hemodialysis, focusing on renal preservation, cardiovascular safety and treatment effectiveness.

The findings demonstrated that therapeutic drug monitoring (TDM) and individualized post-dialysis dosing significantly improved treatment success while reducing nephrotoxicity and cardiovascular complications. Patients managed with optimized dosing experienced higher treatment success rates (82.5% vs. 67.3%), lower nephrotoxicity (11.7% vs. 25.8%), fewer cardiovascular complications (18.3% vs. 31.4%) and superior preservation of residual renal function compared with conventional dosing[28,29]. These findings support the growing evidence that precision antimicrobial therapy is an essential component of cardiorenal management in patients receiving maintenance hemodialysis.

The demographic profile of the present study is consistent with previous reports indicating that CKD predominantly affects older adults with multiple cardiovascular risk factors. More than half of the participants were aged between 50 and 69 years while hypertension and diabetes mellitus were present in 82.7% and 58.2% of patients respectively. These observations closely resemble those reported by the Dialysis Outcomes and Practice Patterns Study (DOPPS), which identified hypertension and diabetes as the leading causes of ESRD worldwide. Many studies demonstrated that cardiovascular disease remains the leading cause of morbidity and mortality among dialysis patients[30]. The substantial prevalence of heart failure (34.5%) observed in the present study further confirms the close interaction between chronic kidney disease and cardiovascular dysfunction, commonly referred to as the cardiorenal syndrome.

In the study , patients demonstrated advanced renal impairment, reflected by markedly elevated serum creatinine, blood urea nitrogen and severely reduced estimated glomerular filtration rate (eGFR). A study highlighted the profound alterations in aminoglycoside pharmacokinetics among critically ill patients with impaired renal function. Reduced renal clearance prolongs aminoglycoside half-life, substantially increasing the risk of nephrotoxicity if conventional dosing regimens are used[31]. Consequently, individualized dose adjustment based on residual renal function and dialysis timing has become increasingly recommended in contemporary nephrology and infectious disease guidelines.

The preservation of residual renal function in approximately 45% of participants is clinically important because even minimal native kidney function contributes significantly to toxin clearance, fluid balance and drug elimination. Previous studies demonstrated that preserved residual renal function independently predicts improved survival, lower hospitalization rates and better quality of life among dialysis patients[32,33]. The present findings are therefore consistent with existing literature emphasizing the importance of protecting residual renal function whenever possible.

One of the principal findings of the study was the significant reduction in aminoglycoside-induced nephrotoxicity among patients receiving therapeutic drug monitoring. Nephrotoxicity occurred in only 11.7% of patients undergoing TDM compared with 26.0% in those managed conventionally. Similarly, increases in serum creatinine and escalation of dialysis frequency were significantly less common in the monitored group.Many researches demonstrated that individualized aminoglycoside dosing guided by serum drug concentrations markedly decreases nephrotoxicity without compromising antimicrobial efficacy[34]. The Kidney Disease: Improving Global Outcomes (KDIGO) recommendations also advocate individualized dosing and close monitoring of nephrotoxic medications in patients with advanced CKD to minimize further renal injury. The present study therefore provides additional clinical evidence supporting routine implementation of therapeutic drug monitoring in dialysis populations.

Cardiovascular disease remains the predominant cause of mortality among patients with ESRD, accounting for nearly half of all deaths in dialysis populations. The current study demonstrated a high prevalence of hypertension, coronary artery disease, left ventricular hypertrophy and heart failure. Importantly, therapeutic drug monitoring was associated with significantly lower rates of

arrhythmias, intradialytic hypotension, heart failure exacerbations, elevated cardiac troponin-I levels and cardiovascular-related hospitalizations[35]. Although aminoglycosides are not directly cardiotoxic, inappropriate dosing may contribute indirectly to electrolyte disturbances, fluid imbalance and systemic inflammatory responses that increase cardiovascular instability. Optimized dosing minimizes these risks by preventing excessive drug accumulation and facilitating better infection control.

Previous studies have highlighted the close interaction between renal dysfunction and cardiovascular disease emphasizing that interventions preserving renal function frequently improve cardiovascular outcomes as well. The current findings support this concept of integrated cardiorenal management[36,37].

Treatment success exceeded 80% among patients receiving therapeutic drug monitoring, significantly higher than among those managed without monitoring. Infection resolution and clinical cure rates were similarly favorable, while hospital mortality remained relatively low despite the high-risk nature of the study population. Comparable observations have been reported by a study that demonstrated that pharmacokinetic-guided antimicrobial dosing improves microbiological eradication and clinical recovery among critically ill patients[38]. Likewise another one emphasized that individualized antimicrobial therapy increases therapeutic efficacy while reducing toxicity, particularly in patients with altered drug clearance such as those receiving renal replacement therapy.

Multivariable logistic regression demonstrated that therapeutic drug monitoring was the strongest independent predictor of favorable outcomes, increasing the likelihood of successful treatment nearly threefold. Individualized post-dialysis dosing, preserved residual renal function, controlled systolic blood pressure, and preserved left ventricular ejection fraction also independently improved outcomes.Conversely, advanced age, diabetes mellitus, and pre-existing heart failure significantly reduced the probability of favorable outcomes[39].

The present study has several important clinical implications as routine therapeutic drug monitoring should become standard practice whenever aminoglycosides are administered to patients with CKD or ESRD receiving intermittent hemodialysis. Secondly, aminoglycoside dosing should always be individualized according to residual renal function, dialysis schedule and patient-specific pharmacokinetic characteristics rather than using fixed dosing regimens. Regular monitoring of renal biochemical parameters, serum drug concentrations, electrolyte status and cardiovascular function may substantially improve patient safety and therapeutic outcomes.

STRENGTHS AND LIMITATION OF STUDY

A major strength of this study is the comprehensive evaluation of both renal and cardiovascular outcomes following individualized aminoglycoside dosing in a well-defined study of CKD and ESRD patients undergoing intermittent hemodialysis. The study also incorporated therapeutic drug monitoring, objective laboratory parameters and multivariable regression analysis to identify independent predictors of favorable outcomes.

Several limitations should be acknowledged. The cross-sectional design limits causal inference between optimized dosing strategies and long-term clinical outcomes. The study was conducted in tertiary care hospital which may limit the generalizability of findings to community healthcare settings. Future multicenter prospective studies and randomized controlled trials are warranted to validate these findings.

CONCLUSION

The present study demonstrate that individualized aminoglycoside dosing based on renal function, dialysis timing and therapeutic drug monitoring significantly improves both renal and cardiovascular outcomes in patients with chronic kidney disease and end-stage renal disease undergoing intermittent hemodialysis. Precision dosing strategies were associated with higher treatment success, lower aminoglycoside-induced nephrotoxicity, preservation of residual renal

function and significant reductions in cardiovascular complication. Therapeutic drug monitoring emerged as the strongest independent predictor of favorable cardiorenal outcomes while individualized post-dialysis dosing, preserved residual renal function and controlled blood pressure further enhanced clinical recovery. In contrast, advanced age, diabetes mellitus and pre-existing heart failure were associated with poorer outcomes. These findings reinforce current evidence supporting precision antimicrobial therapy and highlight the importance of integrating nephrology, infectious disease, cardiology and clinical pharmacy expertise to optimize aminoglycoside therapy. Routine implementation of therapeutic drug monitoring and individualized dosing protocols should be considered standard practice for CKD and ESRD patients receiving intermittent hemodialysis to maximize efficacy, minimize toxicity, and improve long-term cardiorenal outcomes.

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