

CASE REPORT

Pharmacokinetically Guided Pre-dialytic Administration of Amikacin in a Haemodialysis Patient with Resistant Infections: A CARE-compliant Case Report

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Abstract

Introduction: Managing carbapenem-resistant *Enterobacterales* (CRE) in haemodialysis patients is challenging due to the narrow therapeutic index of aminoglycosides. We report a case of a 59-year-old Malaysian male with end-stage renal disease (ESRD) and a severe CRE *Klebsiella pneumoniae* infection who was managed with a pharmacokinetically guided pre-dialytic amikacin strategy. **Case Presentation:** The patient initially failed conventional post-dialysis dosing, resulting in sub-therapeutic peaks and a toxic trough of 15 µg/mL. We switched to a pre-dialytic regimen (6–7 mg/kg), utilising high-flux dialysis as a "controlled clearance" mechanism. This achieved a bactericidal C_{max} of 29.6 µg/mL, a safe trough of 9.2 µg/mL, and average AUC₂₄ ranging from 332–399.8 mg.h/L. The patient tolerated extended pre-dialysis drug exposure of up to 10.5 hours without clinically apparent ototoxicity. However, the patient was readmitted at Day 65 with septic shock and died at Day 82; this death was not attributed to amikacin toxicity.

Conclusion: This case suggests that pre-dialytic dosing may provide a safe, operationally flexible method to achieve critical pharmacokinetic/pharmacodynamic (PK/PD) targets (C_{max}/MIC 8–10) in complex CRE infections, warranting further investigation in larger studies.

Keywords: Amikacin, end-stage renal disease, therapeutic drug monitoring, pre-dialysis, case report



Introduction

Aminoglycosides remain a cornerstone of treatment for severe Gram-negative infections, including multidrug-resistant (MDR) *Pseudomonas aeruginosa* and Carbapenem-resistant *Enterobacterales* (CRE).[1] As concentration-dependent bactericidal agents, their efficacy is best predicted by the ratio of peak concentration to minimum inhibitory concentration ($C_{\max}/MIC$), typically targeting a ratio of 8–10.[2-3] Furthermore, the 24-hour area under the concentration-time curve (AUC_{24}) is vital for optimising clinical outcomes and monitoring toxicity exposure; for Amikacin, AUC_{24} ranging 160-200 mg.h/L is often targeted to ensure efficacy and prevent toxicity.[4] In patients with normal renal function, this is achieved through extended-interval dosing (EID), which maximise the $C_{\max}$ while allowing for a drug-free interval to minimise the risk of nephrotoxicity and ototoxicity.[5]

However, implementing EID in patients with end-stage renal disease (ESRD) on haemodialysis (HD) presents a significant clinical challenge [6-7]. Conventional practice in Malaysia and many global centres involves post-dialysis administration. This approach often utilises lower doses, for example 2mg/kg to 3mg/kg, to prevent toxic accumulation between dialysis sessions [8-11], which frequently results in sub-therapeutic $C_{\max}$ and poor clinical outcomes in high-acuity infections.[8,12]

Recently, pre-dialytic administration has emerged as a pharmacokinetically guided alternative to conventional dosing. [7, 13-16] By administering a full dose, such as 7.5mg/kg, shortly before a dialysis session, clinicians can achieve the target $C_{\max}$ necessary for maximal bactericidal activity, followed by rapid drug clearance via HD to bring the trough level ($C_{\min}$) within the safe range of < 10 µg/mL, as well as containing the AUC within 140-240 mg.h/L over 48 h. [7, 14-16]

While this strategy is incorporated into the Malaysia National Antibiotic Guideline,[17] its clinical application remains minimal and is largely restricted to treating non-tuberculous

mycobacterial (NTM) infections in specialised centres, such as Hospital Kuala Lumpur.

Furthermore, most current literature and guidelines typically suggest a narrow exposure window of 2–4 hours pre-dialysis.[7,13-14] Consequently, there is a lack of widespread implementation for other resistant nosocomial pathogens and a significant data gap regarding the safety and feasibility of longer exposure intervals. This case report details the clinical course of a complex polymicrobial bone and soft tissue infection involving CRE in an ESRD patient. We describe the transition from failed post-dialysis dosing to a therapeutic drug monitoring (TDM)-based pre-dialytic strategy, and we hypothesise that exposure durations of up to 10 hours can be tolerated to achieve optimal pharmacokinetic targets, which are $C_{\max}$, $C_{\min}$, and AUC_{24} , without clinically apparent ototoxicity. We emphasise that this is a single case observation and that the findings are hypothesis-generating.

Case presentation

A 59-year-old Activities of Daily Living (ADL) independent male (75 kg) presented with reduced effort tolerance, shortness of breath, and blackish discoloration of the right fifth toe. His history was significant for ESRD and Chronic Myelogenous Leukaemia (CML) managed with Asciminib. His demographics, clinical characteristics, comorbidities, and dialysis parameters are summarised in Table 1.

On admission, the patient had a markedly elevated C-reactive protein (CRP) of 262 mg/L and anaemia [haemoglobin (Hb) 6.6 g/dL]. He was initially treated for wet gangrene with IV Ampicillin/Sulbactam (3g OD). Due to a lack of clinical improvement and raising total white blood cell (TWBC) count ($8.0 - 10.7 \times 10^9/L$), he underwent a Ray's amputation on Day 10. Intra-operative bone and tissue cultures identified a polymicrobial infection involving *Pseudomonas mosselii* and CRE *Klebsiella pneumoniae*. On Day 15, while the total white blood cell (TWBC)

count was $9.0 \times 10^9/L$, antibiotic therapy was escalated to include IV Tigecycline, Ciprofloxacin, and post-dialysis IV Amikacin. Following this escalation, the systemic inflammatory markers improved, with the TWBC count dropping to $4.9 \times 10^9/L$ by Day 19. However, the localised wound condition continued to deteriorate, becoming increasingly sloughy and necrotic. Due to the failure of localised infection control, the orthopaedic team decided on Day 19 to proceed with a below-knee amputation (BKA). To maximise the bactericidal efficacy of Amikacin during this critical pre-operative period, the dosing strategy was concurrently switched to a pre-dialytic administration.

The BKA was performed on Day 23. Following the transition to pre-dialytic Amikacin and the definitive surgical intervention, the TWBC count remained stable between $4.1 - 5.2 \times 10^9/L$, and CRP levels normalised. The patient was discharged 7 days post-BKA with a clean, healing wound. However, 35 days post-discharge, the patient was readmitted with an infected BKA stump and septic shock; he declined further surgical intervention and was discharged at his own risk, subsequently passing away on Day 82. A detailed chronological summary of the clinical progression, surgical interventions, and the transition between Amikacin dosing strategies is provided in the integrated timeline (Table 2).

Diagnostic assessment

Intra-operative bone and tissue cultures at Day 10 identified a polymicrobial infection involving CRE *Klebsiella pneumoniae* and *Pseudomonas mosselii*. Qualitative disk diffusion classified both these isolates as susceptible to Amikacin, implying unmeasured MICs at or below the updated Clinical and Laboratory Standards Institute (CLSI) boundary breakpoint of $\leq 4 \mu g/mL$. [18] Actual MIC values were not determined, which is a limitation of this case. Maximising concentration-dependent killing against these Gram-negative pathogens requires an optimal C_{max}/MIC ratio of 8-10.[2] Because

typical surveillance data show that susceptible isolates exhibit true MIC values tightly clustered between $1-2 \mu g/mL$, [18] and taking into consideration this is a severe deep-seated infection, an empirical target C_{max} 25-35 $\mu g/mL$ was established. This optimised range ensured a highly effective therapeutic ratio exceeding 8 for both strains simultaneously, while safely capping the upper exposure ceiling to minimise systemic accumulation risks in an anuric patient.

Therapeutic intervention

Following the clinical failure of conventional post-dialysis dosing, which resulted in a toxic trough of $15 \mu g/mL$, a pharmacokinetically guided pre-dialytic strategy was initiated. Amikacin doses of 450-500mg (6-7mg/kg) were administered via a 60-minute intravenous infusion prior to HD sessions utilising an Almedico 1.8 High-flux polysulfone membrane dialyser ($1.8m^2$, Q_b : 200mL/min, Q_d : 500mL/min). To ensure safety, specific dialyser settings and ultrafiltration rates were closely monitored (Table 4) to facilitate adequate drug removal during each 3 to 4-hour session.

Bayesian pharmacokinetic modelling via TDMx software [19] characterised the patient's baseline inter-dialytic parameters, revealing an expanded volume of distribution (V_d) of 26.4L (0.352L/kg) and a profoundly restricted inter-dialytic clearance (CL_{inter}) of 0.47L/h (K_e : $0.0178 hr^{-1}$), corresponding to an extended baseline half-life ($t_{1/2}$) of 38.9 hours. This expanded V_d directly reflects the hypervolaemia and fluid shifts characteristic of ESRD, justifying the initial high pre-dialytic dose to overcome volume dilution and achieve a highly effective, bactericidal peak (C_{max}) of 29.6 $\mu g/mL$. To evaluate machine performance, manual engineering calculations were applied to the active operational flow rates (Q_b : 12L/h volume), assuming a typical high-flux Amikacin extraction efficiency ratio of 33.3%. This yielded a robust intra-dialytic clearance (CL_{intra}) of 4.0L/h, accelerating the elimination rate constant ($K_{e_{dialysis}}$) to $0.152hr^{-1}$ and

collapsing the functional half-life to just 4.6 hours during active machine runtime.

During the initial phase (Days 19–26), the 500mg cycles achieved a robust average AUC_{24} of 399.8 mg.h/L to maximise early bactericidal pressure against the CRE pathogen. This AUC_{24} is above the conventional target of 160–200 mg.h/L for efficacy and toxicity prevention,[4] but is within the higher range proposed for severe infections with elevated MICs. However, the safety of such high AUC_{24} in anuric ESRD patients is not well-established, and this remains a limitation of our case. On Day 27, a pharmacokinetic-guided titration was implemented to reduce the dose to 450mg. This adjustment factored the individual V_d against the accumulated background residual trough (10 μ g/mL), proving that a 450mg dose would provide a safe incremental boost of 17.05 μ g/mL to hit a therapeutic peak of 27.05 μ g/mL with expected C_{min} 6.7 μ g/mL, while safely moderating the overall average AUC_{24} down to 332 mg.h/L. This safer dose adjustment ensured the drug reached effective, bacteria-killing levels while strictly protecting the patient from toxic accumulation. TDM confirmed that this pre-dialytic approach successfully corrected systemic exposure, maintaining stable, non-toxic troughs ranging from 9.2 to 10 μ g/mL across a wide variance of post-dialysis sampling times (7 to 32.5 hours). The full pharmacokinetic profile is illustrated in Figure 1.

The strategy demonstrated significant operational flexibility, allowing for extended pre-dialysis exposure durations of 6.9-10.5 hours. Even during a singular 57-hour exposure caused by the cancellation of an HD session due to a surgical procedure (BKA on Day 23), the trough level measured after the subsequent dialysis session remained safely at the upper therapeutic limit of 10 μ g/mL. Throughout this period of high-dose exposure, no clinical evidence of auditory or vestibular toxicity was observed. However, formal audiometry was not performed, so subclinical ototoxicity cannot be definitively ruled out.

Adverse events

Throughout the duration of Amikacin therapy, the patient was closely monitored for potential aminoglycoside-related toxicities. Although baseline and follow-up formal audiometry were not performed due to the patient's acute clinical condition, the patient was specifically queried for symptoms of ototoxicity at each clinical review. The patient consistently denied experiencing tinnitus, hearing loss, or vestibular symptoms such as dizziness or ataxia. However, the absence of serial audiograms means that subclinical cochleotoxicity cannot be definitively excluded. Regarding electrolyte monitoring, a rise in serum potassium to 5.6 mmol/L (from a baseline of 4.6 mmol/L) was noted on Day 24, five days after the initiation of pre-dialytic dosing. This was managed with an insulin-dextrose "chase". However, potassium levels remained elevated, ranging between 5.0 and 5.5 mmol/L until the patient was discharged on Day 30. Upon readmission on Day 41, the serum potassium remained high at 5.5 mmol/L despite the discontinuation of Amikacin twelve days prior. Given that aminoglycoside-induced nephrotoxicity typically manifests as electrolyte wasting (such as hypokalaemia or hypomagnesemia) and that the hyperkalaemia persisted long after the drug's elimination, this derangement was deemed not attributable to Amikacin. No other electrolyte disturbances, such as hypomagnesemia, were observed, nor were there any infusion-related reactions, phlebitis, or allergic responses reported during the pre-dialytic administration cycles.

Follow-up and outcomes

The transition to a pre-dialytic Amikacin strategy, combined with the right BKA, resulted in an initial stabilisation of the patient's clinical status. However, we acknowledge that surgical source control (BKA) and concurrent antibiotics (tigecycline and ciprofloxacin) were also major contributors to this outcome, and the relative contribution of the amikacin strategy alone cannot be determined. Following the switch to

pre-dialytic dosing, the TWBC count decreased from $10.7 \times 10^9/L$ to $3.9 \times 10^9/L$. The surgical wound remained clean, permitting discharge at 7 days post-operation. Residual renal function, monitored via daily urine output, showed variability during the primary admission. Output ranged from 50 -500 mL/day prior to the initiation of pre-dialytic Amikacin to between anuria and 650 mL/day following the intervention, suggesting no immediate deleterious effect on the remaining renal tissue.

Regarding long-term progression, the patient was readmitted on Day 41 due to a dislodged internal jugular catheter (IJC). At this stage, his functional status was semi-independent, with the patient performing ADL using a walking stick. Although the patient had become anuric, the BKA stump remained clean with no signs of re-infection; the TWBC count ranged from $3.0 -3.7 \times 10^9/L$ throughout this admission. Following successful IJC reinsertion, the patient was discharged on Day 48.

On Day 65, the patient was readmitted from a district hospital in septic shock secondary to hospital-acquired pneumonia and an infected BKA stump, with a TWBC count of $13.8 \times 10^9/L$ and CRP of 350 mg/L. Diagnostic workup identified advanced peripheral vascular disease (PVD) with infrapatellar artery thrombosis, resulting in poor stump recovery and the exhaustion of all viable vascular access sites for HD. Consequently, the patient was no longer a suitable candidate for long-term renal replacement therapy. Additionally, the patient's CML was re-diagnosed as refractory to treatment with a high risk of transformation to acute leukaemia, for which further therapy offered minimal benefit. After refusing a recommended Above-Knee Amputation (AKA), the patient was discharged at his own risk on Day 70 and passed away at a district hospital on Day 82. The cause of death was septic shock secondary to hospital-acquired pneumonia and infected BKA stump, with refractory CML; it was not attributed to amikacin toxicity. During both readmissions, no audiometry was performed. However, the patient

consistently denied tinnitus or hearing loss by symptom inquiry. The longitudinal trend of serial laboratory investigations, Amikacin TDM and the corresponding clinical interventions are summarised in Table 2.

Discussion

CRE infections present a catastrophic clinical threat in acute care, frequently requiring the use of aminoglycosides like Amikacin as a definitive backbone therapy.[18,20] However, managing high-dose aminoglycoside regimens in patients with ESRD on intermittent HD is a notorious clinical dilemma. Achieving the high C_{max} necessary to overcome elevated MIC requires aggressive dosing, which routinely triggers dangerous systemic drug accumulation and severe ototoxicity due to the complete absence of native renal clearance.[8,21] This narrow therapeutic window creates an intense clinical conflict: standard empirical dosing tables almost universally result in therapeutic failure due to under-dosing, while standard maintenance regimens fail to adapt to the highly volatile fluid shifts and altered tissue volumes characteristic of surgical ESRD patients.[2,8]

Pharmacokinetic divergence (Pre-HD vs. Post-HD dosing)

The physiological and mechanical differences between post-dialysis and pre-dialysis administration fundamentally alter their respective pharmacokinetic profiles.[14,21] Under conventional post-HD dosing, small maintenance doses are introduced into a cleared intravascular space that has been heavily contracted by fluid removal via ultrafiltration.[8,16] This mechanism highlights a critical inter-dialytic shift in fluid physiology with ultrafiltration actively reduces extracellular fluid to reach the patient's dry weight, thereby temporarily contracting the functional V_d . While a contracted volume theoretically requires less drug mass to elevate serum concentrations, post-HD dosing remains structurally constrained by

the patient's prolonged inter-dialytic half-life (38.9 hours) [21] that it completely fails to generate commanding serum concentrations needed to overcome high-MIC pathogens.[8,16] The limitations of this approach are clearly demonstrated by tracking the patient's multi-dose timeline. Following an initial post-HD dose, the patient's prolonged baseline inter-dialytic half-life (38.9 hours)[21] left a highly elevated serum concentration of 15µg/mL at 6 AM on Day 16.

Accounting for baseline inter-dialytic decay, the level would drop to 13.48µg/mL by the start of HD at 12 noon. Although the 4-hour high-flux session, by estimation based on intradialytic K_e , would successfully clear the serum levels down to a post-dialysis baseline of 7.33µg/mL, mass-balance equations ($\text{Dose} = \Delta C \times V_d$) [23] indicated that a highly restricted maintenance dose of only 125mg could be safely administered to avoid exceeding safe toxicity thresholds. Pharmacokinetic simulations demonstrated that while pushing a post-HD dose to its absolute mathematical ceiling (355mg) could theoretically decay to a target trough of 9.5µg/mL (toxic limit <10µg/mL) [8,22] over a 44-hour window, it presents severe clinical risks. It leaves zero safety margin for unexpected fluid fluctuations or scheduling delays, and more importantly, the resulting peak concentration (estimated 20.8 µg/mL) still falls short of the commanding 25-35µg/mL target for CRE. Conversely, our pre-HD strategy introduces an aggressive dose (500mg) into an expanded, fluid-overloaded pre-dialytic V_d (26.4L). This safely capitalises on concentration-dependent principles to drive a true bactericidal peak (29.6µg/mL), utilising the subsequent high-flux session to artificially collapse the drug's half-life to 4.6 hours during runtime to clear excess systemic exposure.[8] This reinforces that modifying post-HD dose sizes cannot overcome its structural pharmacokinetic limitations,[8,21] suggesting that the pre-dialytic strategy may be a more viable option (summarised in Table 3).

Dynamic Volumetric Shifts, Fluid Mechanics, and Accumulation Kinetics

The patient's clinical course highlighted the complex interaction between altered body composition, fluid shifts, and drug accumulation in anuric ESRD. The baseline V_d of 26.4L (0.352L/kg) was determined by indexing the TDMx-derived volume against his initial admission weight of 75kg, as postoperative immobility precluded routine re-weighing following his surgical interventions. Under normal physiological conditions, Amikacin is highly hydrophilic and partitions almost exclusively into extracellular fluids.[11]

In this case, the patient's severe pre-dialytic hypervolemia and anuric tissue oedema acted as an expanded systemic reservoir, diluting serum peaks and driving the V_d significantly above the healthy adult average (0.25L/kg).[11,24] This fluid-driven volume space was highly dynamic, fluctuating dramatically between pre-dialysis days, where fluid overload maximised the V_d space, and post-dialysis days, where mechanical ultrafiltration rapidly contracted the extracellular fluid compartment.[8,16]

Adding to this fluid volatility, the structural nature of the patient's surgical interventions forced sharp deviations in his weight-standardised parameters. While his initial minor right foot Ray's Amputation removed negligible bone and soft tissue, causing no discernible pharmacokinetic shift, the major structural reduction of the unilateral right BKA on Day 23 eliminated exactly 5.9% of total body mass according to Osterkamp's limb-weight estimation data.[25] This indicates that the patient's actual physical post-BKA mass had decreased to approximately 70.6kg, shifting his true standardised V_d upward to 0.374L/kg.

Because Amikacin is predominantly cleared via glomerular filtration, this structural lack of native renal function meant that systemic drug elimination was entirely dependent on intermittent high-flux HD runtime.[21] This absolute reliance on mechanical clearance creates an inter-dialytic 'trough plateau' rather than a

continuous decay slope (a consequence of the drug's half-life extending up to 30–60 hours in functionally anephric patients[21]), a phenomenon starkly visible from Day 23 to Day 26 when the patient was accidentally exposed to an extreme, non-clearing exposure profile following an unexpected HD cancellation, which reset to 9.2 µg/mL following subsequent HD.

Intriguingly, while the mathematical expansion of the standardised post-BKA V_d (0.374L/kg) would theoretically suggest a larger dose requirement to maintain peak concentrations,[11] this persistent anuric trough plateau shifted the overarching clinical priority toward reining in systemic accumulation. By Day 27, multi-dose background retention was driving the cumulative exposure toward a higher AUC_{24} ceiling of 399.8 mg.h/L (standard 160–200 mg.h/L,[4] with up to 600 mg.h/L for MIC 8 mg/L[26]). However, the safety of such high AUC_{24} in anuric ESRD patients is not well-established, and this remains a limitation of our case. This critical accumulation profile perfectly justifies why the regimen was titrated down to 450mg post-BKA. To resolve this, a manual linear pharmacokinetic dose reduction was performed to clear the excess systemic exposure, which was subsequently validated via Bayesian software simulation (TDMx)[19] to ensure it successfully reined in cumulative exposure to a safer AUC_{24} profile of 332mg.h/L and lower pre-HD trough while preserving an optimal bactericidal peak. This clinical evolution underscores that combining manual linear pharmacokinetic principles with real-time Bayesian target optimisation, specifically to balance transient fluid-volume shifts against rising cumulative exposure (AUC) is mandatory to navigate complex surgical disruptions safely.[23]

Operational flexibility and safety resilience

A primary operational advantage of this protocol is its tolerance for extended pre-dialysis exposure intervals. While emerging pre-dialytic strategies in the literature utilise variable administration windows ranging from immediately before to 4

hours prior to the HD session,[7,13] our clinical data demonstrates that a pre-dialysis drug exposure window of up to 10.5 hours can be tolerated without clinically apparent toxicity. This extended timeline grants ward nursing staff substantial workflow flexibility without compromising safety.

The framework's safety resilience was starkly demonstrated on Day 23 when an unexpected operational delay delayed HD for BKA, resulting in an unarranged 57-hour inter-dialytic interval following a 500 mg pre-dialytic dose. Because of the patient's anuria, a stagnant 48-hour exposure plateau was sustained near the C_{max} concentration (29.6µg/mL). Despite this prolonged near C_{max} saturation, the patient experienced zero clinical complications. This clinical tolerance suggests that saturable tissue transport mechanisms[5] combined with individual patient genetic resilience[8] prevented destructive cellular accumulation. Serial clinical tracking throughout an 82-day follow-up confirmed a total absence of tinnitus, hearing loss, or vestibular dysfunction, verifying that hypervolaemic fluid expansion provides a robust safety net during unexpected operational disruptions. However, we emphasise that the absence of audiometry means subclinical ototoxicity cannot be excluded, and the safety of such extended exposure requires confirmation in larger studies.

Limitations

Despite the positive clinical outcomes, several limitations of this study must be acknowledged. First, formal baseline and follow-up objective audiometry were not performed due to the patient's acute clinical instability and urgent surgical requirements. While the patient was actively monitored at every clinical review and consistently denied experiencing tinnitus, hearing loss, or vestibular symptoms, the absence of serial audiograms means that subclinical cochleotoxicity cannot be definitively ruled out. Second, actual MIC values were not determined; disk diffusion was used, which provides only qualitative susceptibility data. This limits the

precision of the PK/PD target attainment analysis. Third, as a single centre case observation, these findings, particularly regarding the safety of an extended 10.5 hours pre-dialysis exposure window, may not be generalisable to all patient populations or different high-flux dialyser membranes. Furthermore, while the exposure metrics were guided by Bayesian pharmacokinetic modelling via the TDMx platform, the underlying population models have not been explicitly validated for the Malaysian population. This demographic may exhibit unique volumetric distribution characteristics, especially when compounded by chronic myeloid leukemia (CML), severe anuric fluid overload, and major lower-limb amputation. Fifth, the patient's clinical improvement cannot be solely attributed to the amikacin strategy, as surgical source control (BKA) and concurrent antibiotics (tigecycline and ciprofloxacin) were also major contributors. Sixth, the AUC₂₄ achieved (332–399.8 mg·h/L) was above the conventional target range of 160–200 mg·h/L, and the safety of such high exposure in anuric ESRD patients is not well-established. Finally, the patient's eventual exhaustion of vascular access due to advanced peripheral vascular disease limited our ability to assess long-term safety outcomes or delayed-onset aminoglycoside toxicity beyond the 82-day follow-up period.

Patient Perspective

Following the switch to the pre-dialytic regimen, the patient reported significant relief from lethargy and localised pain as the infection improved. He found the pre-dialysis timing manageable within the ward routine and experienced no additional discomfort. Motivated by the visible healing of his surgical stump, he remained committed to completing the inpatient therapy to ensure full eradication of the infection.

Conclusion

This case suggests that a pharmacokinetically guided pre-dialytic Amikacin strategy may provide a more viable alternative to conventional

post-dialysis dosing for eradicating resistant pathogens in HD patients. To determine the appropriate dosage under this approach, we utilise the patient's fluid-overloaded, pre-dialytic volume of distribution to safely calculate a high initial dose (6-7mg/kg) capable of achieving target bactericidal peaks ($C_{max}/MIC \geq 8-10$). The subsequent maintenance intervals and dose titrations are then systematically derived by using the high-flux dialyser's operating parameters as a predictable mechanism for controlled drug clearance. Furthermore, our findings suggest that an extended pre-dialysis exposure window of up to 10.5 hours was operationally feasible and clinically tolerated without apparent toxicity. This strategy bridges the gap between efficacy and safety, offering a robust, flexible, and mathematically sound dosing framework for managing complex infections in patients with ESRD. However, this is a single case observation, and the findings are hypothesis-generating. Larger, prospective studies with formal audiology and MIC determination.

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Authors' contribution

CSP contributed to manuscript preparation, data collection, and revisions. SM contributed to manuscript review, editing, and approval of the final version.

Conflict of interest statement

The authors declare there is no funding or conflict of interest to disclose. The first author is under the Malaysia Advanced Clinical Pharmacy Programme (MyACPP- Clinical Pharmacokinetics).

Informed consent to participate

Written informed consent for the publication of this case report was not obtained as the patient had passed away prior to the decision to document the case. To ensure ethical compliance and protect patient confidentiality, formal approval for publication was sought and granted by the **Director General of Health, Malaysia.**

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Table 1. Baseline demographics, clinical characteristics, and dialysis parameters

Parameter	Details
Demographics	
Age/gender	59-year-old male
Weight / BMI	75 kg / 25.4 kg/m ²
Smoking / Alcohol History	Ex-smoker (0.0027 pack-years; ceased 25 years ago) / No history of alcohol intake
Allergy History	No known drug or food allergy
Clinical Characteristics	
Primary Comorbidities	Diabetes Mellitus (single oral hypoglycaemic agent); Hypertension (single antihypertensive agent); CML since 2000, with symptomatic anaemia requiring multiple transfusions; ESRD on regular HD; History of pulmonary TB (smear-negative, completed 7-month regimen 3 months before admission)
ESRD Status	eGFR 15.0 mL/min/1.73m ² ; Residual Urine: 0–500 mL/day (Anuric to Oliguric)
Hearing Status	Normal by symptom inquiry; no pre-existing hearing loss
Regular Medications	Furosemide (withheld before Amikacin initiation)
Baseline Inflammatory Markers	CRP: 262 mg/L; Hb: 6.6 g/dL; Platelets: 93 × 10 ⁹ /L
Dialysis Parameters	
Dialysis Vintage	10 months on HD
Vascular Access Type	Right Internal Jugular Catheter
HD Schedule	Tuesday, Thursday, Saturday
HD Session Length	3–4 hours
Dialyzer Type	Almedico 1.8 High Flux (Polysulfone, 1.8 m ²)
Blood Flow Rate (Qb)	200 mL/min
Dialysate Flow Rate (Qd)	500 mL/min
Ultrafiltration Rate	1.5–2.0 L per session

Abbreviations: BMI, Body Mass Index; CML, Chronic myeloid leukaemia; ESRD, End stage renal disease; HD, haemodialysis; TB, Tuberculosis; eGFR, Estimated glomerular filtration rate; CRP, C-reactive protein; Hb, Haemoglobin; Qb, blood flow rate; Qd, dialysate flow rate.

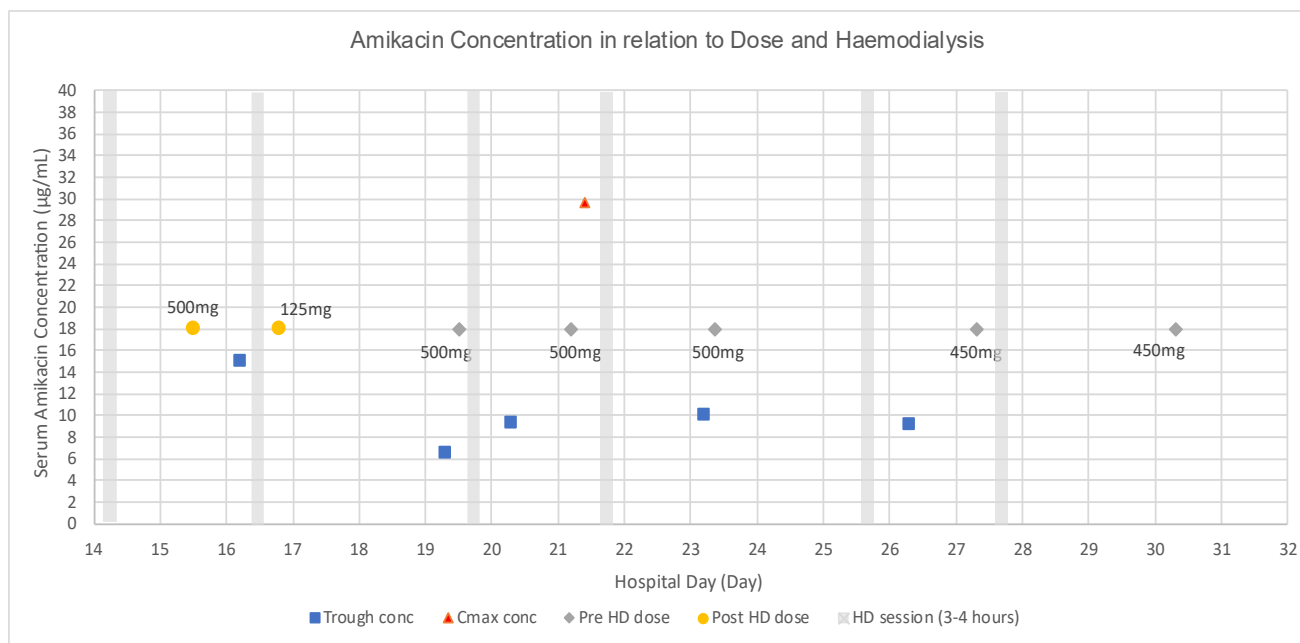


Figure 1. Pharmacokinetic profile of Amikacin concentrations relative to haemodialysis sessions.

The figure illustrates the transition from the initial post-dialysis strategy (Days 15–18) to the optimised pre-dialytic strategy (Days 19–30). Serum Amikacin concentrations (blue dot for trough and red dot for maximum concentration) are measured in µg/mL. The grey vertical shaded bars represent 4-hour high-flux haemodialysis sessions (exception of 3 hours for Day 14 and Day 27). Note the correction of the toxic trough (initially 15 µg/mL) on Day 16 and the successful achievement of a therapeutic peak (29.6 µg/mL) on Day 21 following the switch to pre-dialytic administration. The outlier 57-hour exposure period (Days 23–25) demonstrated that a trough of 10 µg/mL was maintained even with prolonged pre-dialysis exposure.

Table 2. Integrated Clinical Timeline, Amikacin Dosing, and Pharmacokinetic Parameters

Day	Clinical Status & Culture Results	Antibiotics/Amikacin dose & Administration Time	HD Session Timing (Start-End)	Pre-HD exposure Duration	Amikacin TDM & PK Parameters	TWBC (x10 ⁹ /L)	CRP (mg/L)	K ⁺ (mmol/L)
Phase 1: Admission & Initial Management (Day 1–Day 14)								
1	Admission: Blackish discolouration of right fifth toe. Diagnosis: Wet gangrene with right plantar foot abscess	IV Ampicillin/ Sulbactam 3g BD	15:25–19:30 (240 mins)	—	—	8.0	262	4.6
2	Diagnosis updated: Cellulitis	IV Ampicillin/ Sulbactam 3g OD (post-HD)	13:00–17:00 (240 mins)	—	—	—	—	—
3	—	—	07:45–11:45 (240 mins)	—	—	—	—	—
4	—	—	08:40–12:10 (240 mins)	—	—	—	—	—
5	—	—	11:30–14:30 (180 mins)	—	—	—	—	—
10	Ray's amputation. Intra-operative cultures: <i>Pseudomonas mosselii</i> and CRE <i>Klebsiella pneumoniae</i>	—	—	—	—	10.7	—	—
Phase 2: Conventional Post-HD Amikacin Strategy (Day 15–Day 18)								
15	Clinical failure; Last dose of IV Ampicillin/Sulbactam 3g OD	IV Amikacin 500 mg at 12:20 (Post-HD)	08:00–11:00 (180 mins)	—	—	9.0	—	—
16	Wound necrotic	IV Tigecycline 200mg stat & 100mg OD; Tab Ciprofloxacin 750mg OD; IV Amikacin 125 mg at 18:00 (Post-HD)	12:00–16:10 (240 mins)	—	Cmin (06:00): 15 mg/L (Toxic)	—	—	—
Phase 3: Optimised Pre-HD Amikacin Strategy (Day 19–Day 30)								
19	Wound worsening with necrotic patch; surgeon decided on Right BKA. Switch to Pre-HD Strategy	IV Amikacin 500 mg at 10:50	17:45–21:45	6.9 Hours	Cmin (06:00): 6.6 mg/L	4.9	—	—
20	Preparation for BKA surgery	—	—	—	Cmin (06:00): 9.4 mg/L	—	—	—
21	Preparation for BKA surgery	IV Amikacin 500 mg at 06:00	16:30–20:30	10.5 Hours	Cmax (07:30): 29.6 mg/L	—	—	—
23	Right BKA; Intra-operation tissue and bone marrow culture showed no growth	IV Amikacin 500 mg at 06:00	Session Cancelled	57 Hours	Cmin (05:00): 10 mg/L	—	—	—
24	—	—	—	—	—	—	—	5.6
25	Wound Clean	—	15:00–19:00 (240 mins)	—	—	—	—	5.0–5.5

26	—	—	—	—	Cmin (06:00): 9.2 mg/L	—	—	—
27	Wound clean; Improved TWBC	IV Amikacin 450 mg at 07:00	16:30–19:30	9.5 Hours	—	—	—	—
30	Discharge with clean wound	IV Amikacin 450 mg at 06:00; Complete IV Tigecycline and Tab Ciprofloxacin	13:20–17:20	7.3 Hours	—	4.1–5.2	Normalised	5.0–5.5
Post-Discharge								
41	Readmission: Dislodged IJC; BKA wound stump sloughy but no signs of infection; no antibiotics started	—	—	—	—	3.0–3.7	—	5.5
48	Discharged after successful IJC reinsertion at Day 46	—	—	—	—	—	—	—
65	Critical Readmission: Septic shock due to hospital-acquired pneumonia and infected right BKA stump. Fast AF secondary to sepsis. Required inotrope support. Peripheral blood culture: no growth	IV Cefepime 1g OD	Regular HD via FVC IUC (180 mins)	—	—	13.8	350	—
69	Surgeon advised right AKA; patient refused further surgical intervention	—	—	—	—	—	—	—
70	Discharged under DAMA	—	Regular HD via right IUC (240 mins)	—	—	—	—	—
82	Death (septic shock secondary to hospital-acquired pneumonia and infected BKA stump; refractory CML)	—	—	—	—	—	—	—

Abbreviations: HD, haemodialysis; TDM, therapeutic drug monitoring; PK, pharmacokinetic; Cmin, trough concentration; Cmax, peak concentration; BKA, below-knee amputation; TWBC, total white blood cell; CRP, C-reactive protein; K⁺, potassium; IJC, internal jugular catheter; AKA, above-knee amputation; DAMA, discharged against medical advice; FVC, femoral venous catheter; IUC, internal jugular catheter; AF, atrial fibrillation; CML, chronic myelogenous leukemia.

Table 3. Pharmacokinetic calculations and clinical comparison between conventional post-HD and optimised pre-HD amikacin dosing strategies

Parameter	Post-HD Strategy (Initial Course)	Pre-HD Strategy (Optimised Intervention Phase)	Clinical / Pharmacokinetic Rationale
Baseline Vd	Contracted volume: Lowered due to post-session ultrafiltration fluid removal	Expanded volume (26.4 L): Fluid-overloaded, pre-dialytic state	Amikacin is highly hydrophilic; pre-HD dosing utilises fluid expansion to handle higher doses safely.
Concentration at Day 16, 06:00 (before next HD, after first dose IV Amikacin 500 mg on Day 15)	15.0 µg/mL (Toxic baseline buildup)	N/A	Accumulation driven by an extended baseline inter-dialytic $t_{1/2}$ (38.9 hr).
Concentration at Day 16, 12:00 (estimated, before next HD started)	13.48 µg/mL (estimated)	N/A	Natural inter-dialytic decay velocity (K_e : 0.0178 hr ⁻¹) over 6 hours. Formula: $C_2 = C_1 \times e^{(-K_e \cdot t)} = 15 \times e^{(-0.0178 \times 6)} = 13.48 \text{ µg/mL}$
Concentration at Day 16, 16:00 (Post-HD Session)	7.33 µg/mL	N/A	Drop driven by a 4-hour high-flux HD runtime (K_e : 0.152 hr ⁻¹). Formula: $C_2 = C_1 \times e^{(-K_e \cdot t)} = 13.48 \times e^{(-0.152 \times 4)} = 7.33 \text{ µg/mL}$
Resulting Cmax	12.0 µg/mL (targeted)	29.6 µg/mL (actual)	A. Post-HD Cmax must be low to leave a wide, non-toxic safety buffer; Pre-HD allows high Cmax. B. Post-HD failed the target Cmax (25–35 µg/mL) needed to overcome high-MIC CRE pathogens.
Administered / Simulated Dose Size	125 mg given (restricted maintenance dose)	500 mg given (higher maintenance dose)	Post-HD dose must be severely limited to avoid stacking; Pre-HD allows higher dose. Formula: $\text{Dose} = \Delta C \times V_d = (12 - 7.33 \text{ µg/mL}) \times 26.4 \text{ L}$
Calculated Maximum Theoretical Dose	355 mg (absolute mathematical ceiling)	N/A	Pushing post-HD to its absolute limit (estimating trough 9.5 µg/mL) yields a peak of only 20.8 µg/mL and leaves zero safety buffer. Formula: A. $C_2 = C_1 \times e^{(-K_e \cdot t)}$; $9.5 = C_{\text{max}} \times e^{(-0.0178 \times 44)}$; $C_{\text{max}} = 20.8 \text{ µg/mL}$. B. $\text{Dose} = \Delta C \times V_d = (20.8 - 7.33) \times 26.4 = 355 \text{ mg}$
Target AUC ₂₄	N/A	399.8 → 332 mg·h/L	Step-down titration to 450 mg successfully controlled accumulation while retaining efficacy. Calculation method: AUC by TDMx; Dose by manual PK calculation. Note: AUC ₂₄ achieved was above the conventional target of 160–200 mg·h/L; safety of high AUC ₂₄ in anuric ESRD is not well-established.

Abbreviations: HD, haemodialysis; Vd, volume of distribution; N/A, not available; $t_{1/2}$, half-life; hr, hour; C, concentration; µg/mL, micrograms per millilitre; K_e , elimination rate constant; Cmax, peak concentration; MIC, minimum inhibitory concentration; CRE, carbapenem-resistant Enterobacterales; ΔC , incremental concentration; AUC₂₄, area under the curve over 24 hours; ESRD, end-stage renal disease.

Table 4. Detailed pharmacokinetic parameters and dialysis operational settings

Category	Parameter	Specification / Value
PK Parameters*	Ke (hr ⁻¹)	0.0178 / 0.152 (interdialytic / intradialytic)
	Amikacin CL (L/hr)	0.47 / 4.0 (interdialytic / intradialytic)
	t _{1/2} (hr)	38.9 / 4.6 (interdialytic / intradialytic)
	Vd	26.4 L (0.352 L/kg); post-BKA: 0.374 L/kg
	C _{max} Sampling Time	30 minutes post-infusion
	C _{min} Sampling Time	Pre-dialysis (7–32.5 hours after previous dialysis)
Dialyser Technical Data	Pre-HD Exposure Range	6.9–10.5 hours (clinical routine)
	Dialyser Model	Almedico 1.8 High Flux
	Membrane Material	High-flux Polysulfone
	Surface Area	1.8 m ²
Operational Settings	Urea KoA	≈1000 mL/min
	Blood Flow Rate (Q _b)	200 mL/min
	Dialysate Flow Rate (Q _d)	500 mL/min
	Ultrafiltration Rate	1.5–2.0 L per session
	Session Duration	180–240 minutes
	Amikacin Infusion Time	60 minutes (1 hour)

Calculated by TDMx. Abbreviations: PK, pharmacokinetic; Ke, elimination rate constant; hr, hour; CL, clearance; t_{1/2}, half-life; Vd, volume of distribution; C_{max}, peak concentration; C_{min}, trough concentration; Pre-HD, pre-haemodialysis; KoA, mass transfer area coefficient for urea; Q_b, blood flow rate; Q_d, dialysate flow rate.

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