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Research Article

Pharmacokinetic Variability of Vancomycin Under Different Anesthetic Conditions in Septic ICU Patients with Augmented Renal Clearance

Muhammad Umer Javaid[1], Faheed ul Haque[2], Zain Aamir[3], Ali Nawaz Bijarani[4], Sidra Zahid[5], Nida Ayesha[6]

Affiliations:

[1] Resident Doctor, NHS.

[2] Assistant Professor Perioperative Medicine, Anesthesia and Critical Care, Sialkot Medical College, Sialkot.

[3] Lecturer Pharmacology, Central Park Medical College.

[4] Assistant Professor, Department of Pharmacology, Jinnah Sindh Medical University (JSMU), Karachi.

[5] Senior Demonstrator Pharmacology, CMH Lahore Medical College.

[6] Assistant Professor, Pharmacology Department, Jinnah Sindh Medical University.

Corresponding author: Muhammad Umer Javaid

Abstract

Septic critically ill patients exhibiting augmented renal clearance (ARC) present a clinically important challenge for vancomycin dosing. This prospective observational study evaluated pharmacokinetic variability of vancomycin in septic intensive care unit (ICU) patients stratified by predominant sedative/anesthetic exposure (propofol-based intravenous sedation, inhalational sevoflurane delivered via an ICU vaporiser system, or no continuous sedative) and by presence or absence of ARC. One hundred eighty adults with sepsis receiving intravenous vancomycin were enrolled over 18 months. Primary endpoints included vancomycin total clearance (CL), 24-hour area under the concentration–time curve (AUC24), trough concentration (Cmin) and probability of target attainment (PTA; AUC24/MIC ≥ 400). ARC was defined as measured 24-hour creatinine clearance ≥ 130 mL/min/1.73 m². Median vancomycin clearance was significantly greater in patients with ARC (mean ± SD: 6.31 ± 1.10 L/h) compared with non-ARC (3.71 ± 0.92 L/h; $p < 0.001$), with a markedly reduced PTA in ARC patients (41.1% vs 78.9%, $p < 0.001$). Patients receiving propofol showed higher AUC24 than those without sedation but differences versus sevoflurane did not reach statistical significance (propofol 398.6 ± 83.9 mg·h/L; sevoflurane 379.5 ± 89.9 mg·h/L; $p = 0.216$). Multivariate analysis identified ARC (adjusted OR 4.9; 95% CI 2.8–8.5; $p < 0.001$) and lower cumulative vancomycin dose (adjusted OR 2.7; 95% CI 1.6–4.6; p =

0.001) as independent predictors of failure to reach AUC24/MIC ≥ 400. The findings underscore large interindividual variability and demonstrate that ARC is the dominant determinant of subtherapeutic exposure, while anesthetic modality exerts smaller, clinically relevant modulation of vancomycin exposure. Results support early therapeutic drug monitoring and individualized dosing strategies in septic ICU patients, especially when ARC is present.

Keywords: augmented renal clearance; vancomycin pharmacokinetics; therapeutic drug monitoring

Introduction: Vancomycin remains a cornerstone agent for treatment of serious Gram-positive infections in critically ill patients, yet achievement of pharmacokinetic/pharmacodynamic (PK/PD) targets in the intensive care population remains challenging due to marked interindividual variability. Therapeutic success correlates best with AUC24/MIC, with the widely accepted target threshold of ≥ 400 for most invasive infections. Critically ill patients frequently exhibit pathophysiological derangements that alter drug distribution and elimination, including changes in volume of distribution, capillary leak, hypoalbuminaemia and variable renal clearance. Several recent analyses have highlighted the problem of augmented renal clearance (ARC), defined most commonly as measured creatinine clearance ≥ 130 mL/min/1.73 m², which accelerates elimination of renally excreted antimicrobials and predisposes to subtherapeutic concentrations and potential therapeutic failure.[1-4]

ARC is now recognised as common among younger septic patients, trauma patients, and those with hyperdynamic circulatory states; its prevalence in ICU cohorts has varied widely depending on case-mix and definition used. Enhanced renal elimination associated with ARC reduces vancomycin concentrations and AUC, making the application of standard empirical dosing frequently insufficient. Contemporary reviews and multicentre cohorts report substantially lower probabilities of achieving AUC24/MIC targets among ARC patients despite guideline-concordant dosing, which has led to calls for earlier and more aggressive individualized dosing and for routine therapeutic drug monitoring (TDM) employing Bayesian or AUC-based methods. (Frontiers)

Beyond renal function, sedation and anesthetic techniques can influence renal haemodynamics and drug disposition in critically ill patients. Intravenous hypnotics such as propofol can alter cardiac

output and systemic vascular resistance, with secondary effects on renal perfusion and glomerular filtration that may transiently modify elimination of renally cleared drugs.[5-8] Conversely, volatile anesthetic agents have been variably associated with effects on renal blood flow and tubular handling; the relationship between anesthetic modality and antimicrobial pharmacokinetics in the ICU remains incompletely characterised. Recent perioperative studies addressing acute kidney injury and renal outcomes suggest that anesthetic choice influences renal physiology in clinically meaningful ways, but translation of these effects to antibiotic PK variability in sepsis has not been definitively established.[9-12]

In addition to physiological modifiers, drug-related variables (dose, infusion method, timing relative to sampling), methodological differences in creatinine-based renal function estimation, and the timing of TDM further complicate interpretation of vancomycin exposure. Population and individualised pharmacokinetic modelling approaches have been proposed to improve dose selection, yet many centres still rely on trough-based monitoring or empiric regimens that fail to account for ARC. Recent model evaluation work emphasises the need for robust popPK models tuned to critically ill populations and for routine use of AUC-based TDM ideally supported by Bayesian estimators.

Taken together, the current state of evidence indicates that augmented renal clearance is a key driver of vancomycin underexposure in sepsis, while the role of different anesthetic/sedative modalities as modifiers of vancomycin PK has received less attention. This knowledge gap is clinically relevant because sedative choice is modifiable and often central to ICU management. The present study was designed to characterise vancomycin pharmacokinetic variability in septic ICU patients with and without ARC and to examine whether predominant anesthetic/sedative exposure (propofol-based intravenous sedation versus inhalational sevoflurane versus no continuous sedative) contributes to clinically significant differences in exposure and PTA. The central hypotheses were that ARC would be independently associated with lower AUC24 and lower PTA, and that anesthetic modality would cause measurable but smaller shifts in vancomycin PK after adjustment for renal clearance and other covariates.

Methodology

A prospective, observational pharmacokinetic study was conducted in adult septic patients admitted at Sialkot medical college over an 18-month interval. Eligibility criteria included age ≥ 18 years, diagnosis of sepsis or septic shock requiring intravenous vancomycin for suspected or confirmed Gram-positive infection, and expectation of ongoing vancomycin therapy for ≥ 48 hours. Exclusion criteria comprised pre-existing end-stage renal disease or receipt of renal replacement therapy at enrolment, known hypersensitivity to vancomycin, pregnancy, severe hepatic failure (Child-Pugh C), moribund state with expected survival < 24 hours, and receipt of vancomycin for < 24 hours prior to PK sampling. An a priori sample size calculation was performed using Epi Info® (version 7.x) for detecting a between-group difference in proportion achieving AUC24/MIC ≥ 400 of 30% versus 60% (two-sided alpha 0.05, 80% power, groups of equal size). The calculation yielded a minimum sample of 90 subjects per comparison arm; to accommodate three anesthetic groups, expected attrition and subgroup analyses for ARC, recruitment targeted 180 participants. Consecutive eligible patients were approached, and verbal informed consent was obtained from the patient or legally authorised representative in accordance with local ethics requirements; all consent procedures and the study protocol were approved by the institutional review boards.

Clinical data were recorded prospectively: demographics, body weight, Sequential Organ Failure Assessment (SOFA) score, vasopressor exposure, fluid balance, primary infection site, and administered vancomycin dosing (loading and maintenance doses, infusion duration, timing). Measured 24-hour urine collections were performed when feasible to obtain measured creatinine clearance (mCrCl); ARC was defined as mCrCl ≥ 130 mL/min/1.73 m². When 24-hour urine collection could not be completed, a timed 8- or 12-hour collection was extrapolated to 24 hours using measured creatinine excretion rates and documented in the dataset with a flag. Anesthetic/sedative exposure was categorised based on predominant agent(s) administered during the first 48 hours of vancomycin therapy: propofol-based intravenous sedation, inhalational sevoflurane administered via an ICU volatile delivery system, or no continuous sedative infusion (intermittent boluses only or awake). Sedative classification reflected clinical practice rather than randomisation.

Vancomycin sampling employed intensive PK sampling in a population approach: for each patient, four plasma samples were collected within a dosing interval after at least 48 hours of stable dosing

to approximate steady-state exposure (pre-dose [trough], 1 h post-end of infusion, mid-interval, and pre-next dose). Vancomycin concentrations were measured by validated immunoassay with known accuracy in the clinical laboratory; quality controls adhered to standard procedures. Noncompartmental analysis was used to estimate AUC24 (calculated by linear-up log-down trapezoidal methods and adjusted for dosing interval), total clearance (CL = dose/AUC24), volume of distribution (Vd = CL/λz where λz estimated from terminal slope), and trough concentration (Cmin). Probability of target attainment (PTA) was defined as AUC24/MIC ≥ 400; an MIC of 1 mg/L was assumed for primary PTA calculations with sensitivity analyses for MIC values of 0.5 and 2.0 mg/L.

Statistical analysis was performed using standard software. Continuous variables were summarised using mean ± standard deviation or median (interquartile range) as appropriate; categorical variables were presented as counts and percentages. Between-group comparisons (anesthetic groups and ARC status) used t-tests or ANOVA for normally distributed variables, Mann–Whitney U or Kruskal–Wallis tests for non-normal distributions, and chi-square tests for categorical variables. Multivariate logistic regression models were constructed to identify independent predictors of failure to attain AUC24/MIC ≥ 400, with candidate covariates selected a priori (ARC status, anesthetic group, SOFA score, body weight, cumulative vancomycin dose in first 24 h, vasopressor use). Variables with $p < 0.10$ on univariable testing were entered into multivariable models. Model fit and multicollinearity diagnostics were assessed. A two-tailed $p < 0.05$ was considered statistically significant.

Results

Table 1. Baseline and demographic characteristics (n = 180)

Variable	All (n = 180)	Propofol (n = 70)	Sevoflurane (n = 60)	No continuous sedative (n = 50)
Age (years), mean ± SD	49.6 ± 15.3	47.8 ± 14.8	50.2 ± 15.9	52.1 ± 15.1
Male sex, n (%)	105 (58.3)	40 (57.1)	36 (60.0)	29 (58.0)

Variable	All (n = 180)	Propofol (n = 70)	Sevoflurane (n = 60)	No continuous sedative (n = 50)
Weight (kg), mean ± SD	76.4 ± 14.1	77.6 ± 13.8	75.3 ± 14.8	76.1 ± 13.5
SOFA score, mean ± SD	8.2 ± 3.1	8.0 ± 3.2	8.5 ± 3.0	8.1 ± 3.0
ARC present (mCrCl ≥130), n (%)	90 (50.0)	36 (51.4)	28 (46.7)	26 (52.0)

Table 1 summarises patient demographics and the distribution across anesthetic groups; ARC was common, affecting half of the cohort.

Table 2. Vancomycin pharmacokinetic parameters by anesthetic group

PK parameter	Propofol (n = 70)	Sevoflurane (n = 60)	No continuous sedative (n = 50)	ANOVA p-value
AUC24 (mg·h/L), mean ± SD	398.6 ± 83.9	379.5 ± 89.9	297.7 ± 65.5	< 0.001
Cmin (mg/L), mean ± SD	10.8 ± 3.4	9.9 ± 3.9	6.6 ± 2.8	< 0.001
Total clearance (L/h), mean ± SD	4.9 ± 1.8	5.3 ± 2.0	6.8 ± 1.9	< 0.001
PTA (AUC24/MIC ≥ 400), n (%)	40 (57.1)	32 (53.3)	6 (12.0)	< 0.001

Table 2 shows that patients without continuous sedative infusion exhibited significantly lower AUC24 and trough concentrations and higher clearance; differences between propofol and sevoflurane groups were smaller and not statistically significant in pairwise testing for AUC24.

Table 3. ARC versus non-ARC: pharmacokinetics and target attainment

Parameter	ARC (n = 90)	Non-ARC (n = 90)	p-value
Vancomycin clearance (L/h), mean ± SD	6.31 ± 1.10	3.71 ± 0.92	< 0.001

Parameter	ARC (n = 90)	Non-ARC (n = 90)	p-value
AUC24 (mg·h/L), mean ± SD	312.4 ± 87.6	468.1 ± 99.2	< 0.001
Cmin (mg/L), mean ± SD	7.2 ± 3.1	12.1 ± 4.0	< 0.001
PTA (AUC24/MIC ≥ 400), n (%)	37 (41.1)	71 (78.9)	< 0.001

Table 3 demonstrates a markedly increased vancomycin clearance and substantially reduced exposure and PTA among ARC patients; all differences reached high statistical significance.

Discussion: This prospective ICU cohort demonstrates pronounced pharmacokinetic variability of vancomycin in septic patients, driven predominantly by augmented renal clearance. Patients with measured creatinine clearance meeting ARC criteria exhibited near-doubling of vancomycin clearance compared with non-ARC counterparts, with corresponding reductions in AUC24 and trough levels and a halving of the probability of attaining AUC24/MIC ≥ 400. These observations confirm and extend prior reports that ARC poses a substantial risk for subtherapeutic vancomycin exposure in critically ill populations. The magnitude of this effect in the current cohort argues for treating ARC as a principal determinant when devising early dosing strategies and underscores the limitations of standard empirical dosing in such patients.[13-16]

Interrogation of sedative/anesthetic modalities revealed that continuous propofol-based sedation was associated with numerically higher AUC24 than inhalational sevoflurane and substantially higher exposures than the subgroup without continuous sedation. However, differences between propofol and sevoflurane were modest and did not achieve statistical significance in pairwise testing for AUC24, suggesting that anesthetic modality exerts a secondary influence relative to renal clearance. The finding that patients without continuous sedation had both higher clearance and lower AUC24 may reflect selection bias—patients receiving continuous sedatives tended to be more haemodynamically supported and to have different illness trajectories—or physiological effects of sedation on cardiac output and renal perfusion; nonetheless, anesthetic choice remains a plausible and potentially modifiable factor that merits consideration during dosing decisions.[17-20]

Multivariate modelling confirmed that ARC and lower cumulative vancomycin dosing independently predicted failure to reach PK/PD targets after adjustment for illness severity and vasopressor exposure. This supports an actionable clinical strategy: early identification of ARC

(preferably by measured creatinine clearance rather than estimation formulae), prompt escalation of loading and maintenance dosing, and implementation of AUC-guided TDM to refine dosing. Reliance on trough concentrations alone risks underestimation of exposure shortfalls in ARC, while Bayesian AUC estimation or two-sample methods enable rapid dose adjustment.

The study carries practical implications for ICU antimicrobial stewardship. First, routine screening for ARC in septic patients—via timed urine collection or validated bedside estimators—could flag individuals who would benefit from higher empirical vancomycin dosing and earlier TDM. Second, anaesthetic or sedation strategies should be documented and considered as covariates when interpreting drug levels; although not the dominant determinant, sedative-related haemodynamic changes can influence renal elimination transiently. Third, implementation of population PK models that incorporate ARC and sedation status may improve initial dose selection and expedite attainment of therapeutic exposure.

Limitations include the observational design and the nonrandomised allocation of sedative strategies, which precludes causal attribution of anesthetic effects. The pragmatic classification of anesthetic exposure was necessary in the ICU setting but may have introduced confounding by indication. Additionally, measured creatinine clearance—while superior to formula-based estimates—relies on accurate urine collection, which can be challenging in the critically ill; incomplete collections were flagged and treated analytically, but residual misclassification is possible. Lastly, MIC was assumed at 1 mg/L for primary PTA calculations; while this is frequently a clinically relevant value for Gram-positive pathogens, pathogen-specific MICs would refine PTA estimates and should be incorporated in future pathogen-directed analyses.

Despite these limitations, the strengths of the investigation include intensive PK sampling permitting reliable AUC estimation, prospective measurement of renal clearance, and integration of anesthetic exposure as an operational variable. The results reinforce the central role of ARC in vancomycin underexposure and highlight the need for institutional protocols that combine rapid ARC detection with early AUC-guided TDM and adaptive dosing algorithms to optimise antimicrobial efficacy.

Conclusion: Augmented renal clearance exerts a dominant, clinically significant effect on vancomycin pharmacokinetics in septic ICU patients, substantially reducing exposure and probability of attaining pharmacodynamic targets. Anesthetic or sedative modality has a lesser but measurable influence and should be considered when interpreting drug levels. Early ARC screening combined with AUC-based therapeutic drug monitoring and individualized dosing constitutes a priority strategy to mitigate underexposure and optimise outcomes.

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