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ORIGINAL RESEARCH

Optimize Vancomycin Dose in Surgical Ward Patients with Augmented Renal Clearance Determined by Chronic Kidney Disease Epidemiology Collaboration Equation

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Background: In the field of postoperative care, infections caused by Gram-positive bacteria pose a major clinical challenge. Vancomycin is a key therapeutic agent whose efficacy is greatly influenced by renal function, particularly by augmented renal clearance (ARC). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR) is an easy and commonly used method to predict ARC; however, it is not well studied to determine vancomycin dose. In this study, we examined the effectiveness of the CKD-EPI equation in determining ARC and optimizing the dose of vancomycin for surgical ward patients.

Methodology: A retrospective observational study was conducted to examine 158 surgical ward patients receiving vancomycin. Data on demographics, medical history, and vancomycin dosing were collected. Renal function was evaluated using the CKD-EPI equation, with ARC defined as eGFR $\geq$ 96.5 mL/min/1.73 m^2. Vancomycin pharmacokinetics were calculated using the ClinCalc tool.

Results: ARC was in 54% of the patients. Compared with patients without ARC, those with ARC were younger and had lower serum creatinine levels. They also required higher vancomycin doses but had lower trough concentrations and 24-hour area-under-the-curve values. A significant correlation was observed between eGFR and vancomycin clearance, with eGFR > 96.5 mL/min/1.73 m^2 necessitating higher vancomycin doses (>45 mg/kg/day) to achieve the desired area under the curve to minimum inhibitory concentration ratio.

Conclusion: For surgical ward patients with CKD-EPI eGFR $\geq$ 96.5 mL/min/1.73 m^2, a vancomycin dosage of >45 mg/kg/day may be recommended to reach effective therapeutic levels. Overall, this study emphasizes the importance of tailoring vancomycin therapy depending on renal function to ensure efficacy and mitigate the risk of antimicrobial resistance in surgical ward patients.

Keywords: augmented renal clearance, vancomycin, surgery

Introduction

Postoperative infection is a common complication of surgery, which may prolong hospitalization and affect prognosis.[1] Gram-positive bacteria are often involved in postoperative infections.[2] With the emergence of drug-resistant strains, vancomycin plays a key role in combating infections caused by Gram-positive bacteria, particularly by *Staphylococcus aureus*.[3–5]

The pharmacokinetic/pharmacodynamic (PK/PD) target of vancomycin is defined as the ratio between the area under the curve (AUC) and the minimum inhibitory concentration (MIC), with an optimal target range of 400 to 600 to ensure efficacy and reduce nephrotoxicity.[4] Optimizing the PK/PD target of antibiotics can improve clinical outcomes.[6] AUC/MIC monitoring is primarily recommended for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections,

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such as bacteremia, infective endocarditis, and pneumonia, due to its stronger correlation with clinical outcomes.[4] It is also preferred for patients at high risk of nephrotoxicity, including critically ill patients, patients with unstable renal function, and those on prolonged vancomycin therapy.[4] Trough-only monitoring is no longer recommended due to the higher likelihood of achieving an AUC/MIC >400 with trough concentrations between 10 and 15 mg/L, and the increased risk of nephrotoxicity when trough concentrations exceed 15 mg/L.[7,8] Moreover, numerous studies have demonstrated that AUC-guided monitoring reduces the risk of nephrotoxicity compared to trough-only monitoring.[9] Currently, only for patients undergoing hemodialysis, pre-dialysis concentrations with a target range of 15–20 mg/L are used instead of targeting AUC/MIC.[10] Therefore, identifying the factors affecting the PK/PD target and promptly adjusting drug dosages are clinically essential.

Postoperative patients may experience increased physiological stress, which increases cardiac output and renal perfusion, resulting in enhanced drug clearance.[11–13] Augmented renal clearance (ARC) is defined as a urinary creatinine clearance rate of ≥130 mL/min/1.73 m^2.[5,11,12] The risk factors for ARC are young age and a low severity-of-illness score on the Sequential Organ Failure Assessment; these risk factors are commonly observed in patients with trauma, burns, acute brain injury, and hematological malignancies.[11,12] Multiple studies have indicated a high likelihood of ARC development in surgical patients, leading to inadequate vancomycin concentrations that increase the risk of treatment failure and drug resistance.[5,14] Currently, ARC is clinically confirmed by collecting 24-hour urine samples to calculate the rate of creatinine clearance, which is labor-intensive and lacks real-time information.[13,15] Among the primary methods used for the rapid assessment of renal function in clinical practice are the Cockcroft–Gault (CG) equation, the four-variable Modification of Diet in Renal Disease (MDRD) equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[16,17] In critically ill patients, the CKD-EPI equation exhibits higher predictive power for ARC compared with the GC and MDRD equations, and it has the most favorable specificity and sensitivity at a cutoff of ≥96.5 mL/min/1.73 m^2.[15] The CKD-EPI equation is also associated with the smallest bias in predicting the therapeutic concentrations of vancomycin.[18] Despite these findings, no studies have yet confirmed the applicability of the aforementioned cutoff in determining ARC and subsequent effect on vancomycin PK/PD target in surgical ward patients. Therefore, in this study, we applied the aforementioned cutoff value of CKD-EPI equation to determine the ARC and its effect on vancomycin dose and PK/PD target in surgical ward patients.

Methods

Study Population

This retrospective observational study was conducted at the National Taiwan University Hospital Yunlin Branch (NTUHYL) from September 2019 to October 2021. Patients who were at least 20 years of age and did not meet any exclusion criteria were included in this study. The exclusion criteria included patients undergoing renal replacement therapy or limb amputation, receiving only 1 ~ 3 doses of vancomycin, using vancomycin via oral solution and lock therapy, lacking vancomycin trough level, not receiving a loading dosage and having a baseline serum creatinine (S_{Cr}) level of greater than 1.3 mg/dL before the initiation of vancomycin treatment, and those admitted to medical wards.[15] Clinical data obtained from the medical records of NTUHYL were anonymized and reviewed by the Research Ethics Committee of NTUHYL. The study protocol was approved by the Institutional Review Board of NTUHYL (20210913RIN). The informed consent was waived because of the retrospective nature of this study and all patient identification was removed. This study was conducted in accordance with the Declaration of Helsinki.

Data Collection and Analysis

The clinical records of all participants were carefully reviewed and documented, including the variables of sex, body weight, height, S_{Cr}, surgical details, intensive care unit (ICU) admission, underlying diseases, mannitol use, vancomycin indication, loading and maintenance doses, and serum trough concentration (within one hour prior to next drug administration). After a minimum of four vancomycin doses, vancomycin serum trough concentrations were measured through a chemiluminescent microparticle immunoassay with an Architect i1000SR immunoassay analyzer (Abbott Laboratories, Abbott Park, Illinois, USA).

Renal function was estimated using the 2009 CKD-EPI equation.[19] ARC was defined as an estimated glomerular filtration rate (eGFR) of 96.5 mL/min/1.73 m^2 or higher. eGFR was differently calculated for men and women depending on their S_{Cr} levels as follows:

For men:

If $S_{Cr} \leq 0.9$, $eGFR = 141 \times (S_{Cr}/0.9)^{-0.411} \times 0.993^{age}$

If $S_{Cr} > 0.9$, $eGFR = 141 \times (S_{Cr}/0.9)^{-1.209} \times 0.993^{age}$

For women:

If $S_{Cr} \leq 0.7$, $eGFR = 144 \times (S_{Cr}/0.7)^{-0.329} \times 0.993^{age}$

If $S_{Cr} > 0.7$, $eGFR = 144 \times (S_{Cr}/0.7)^{-1.209} \times 0.993^{age}$

PK and PD Analysis

The PK/PD target for vancomycin is currently determined using the AUC/MIC ratio, with a recommended range of 400–600 for optimal efficacy and minimal risk of nephrotoxicity.[4] In this study, we used the vancomycin calculator of ClinCalc to estimate AUC and vancomycin clearance (https://clincalc.com/vancomycin).

This calculator, based on the vancomycin population pharmacokinetic (PK) model from Buelga's study, which was developed in patients with hematological malignancies known to exhibit ARC, utilizes Bayesian methods and patient-specific parameters (age, height, weight, sex, and S_{Cr}), along with vancomycin dose, frequency, and serum trough concentration, to estimate the AUC and vancomycin clearance.[20] The first serum trough concentration after empirical dosing was used for AUC calculation.

Statistical Analysis

Continuous data are presented as median along with interquartile ranges (IQR), with the minimum and maximum values specified following the semicolon, and categorical data are presented as numbers and percentages. The Kolmogorov–Smirnov test was used to assess normality. If the continuous data were normally distributed, an independent *t*-test was performed; otherwise, the Mann–Whitney *U*-test was applied to compare the difference between those with and without ARC. For categorical data, the Chi-square test or Fisher's exact test was used. Spearman correlation coefficient (*r*) was used to determine the correlation between eGFR and vancomycin clearance. A *p* value of ≤0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics version 23 (IBM, Armonk, NY, USA) and graphing was conducted by GraphPad Prism (version 10.1.2, GraphPad Software, Boston, USA).

Results

This retrospective study was conducted on 158 patients who received intravenous vancomycin and whose serum levels were monitored from October 2019 to September 2021 (Figure 1). Among these patients, 67.7% (107 patients) were men, 87.3% (138 patients) had undergone surgery, 40.5% (64 patients) had been treated in an ICU, and 54% (85 patients) had ARC. The vancomycin maintenance dose was set to 33.0 mg/kg/day, with a median trough concentration of 14.0 mg/L (Table 1).

Patients were divided into two groups: an ARC group and a non-ARC group. Compared with the non-ARC group, the ARC group was younger (mean age: 51 vs 70 years, $p < 0.001$), had lower S_{Cr} levels (0.6 vs 0.9 mg/dL, $p < 0.01$), and had a lower incidence of cardiovascular disease (31.8% vs 67.1%, $p < 0.001$) and diabetes (22.4% vs 37.0%, $p = 0.04$). The ARC group also had more trauma-related admissions (31.8% vs 13.7%, $p = 0.008$) and more frequent mannitol treatment (25.9% vs 9.6%, $p = 0.008$) compared with the non-ARC group. In terms of vancomycin treatment, the ARC group received a higher maintenance dose (42.0 vs 28.0 mg/kg/day, $p < 0.001$) but had significantly lower trough concentrations (11.7 vs 15.4 mg/L, $p = 0.001$) and 24-hour AUC (AUC_{24h}) values (408 vs 467 mg/L x hr, $p = 0.008$) compared with the non-ARC group (Table 2). In terms of the maintenance dose, the ARC group exhibited lower AUC_{24h} values at both ≤30 mg/kg/day (286 vs 453 mg*h/L, $p < 0.001$) and 30–45 mg/kg/day (395 vs 503 mg/L x hr, $p < 0.01$) compared with the non-ARC group (Figure 2). The ARC group had a larger proportion of patients with AUC_{24h} values below 400 compared with the non-ARC group (47% vs 26%, $p = 0.007$). As shown in Figure 3, a significant positive correlation was observed between eGFR and vancomycin clearance ($r = 0.711$, $p < 0.001$).

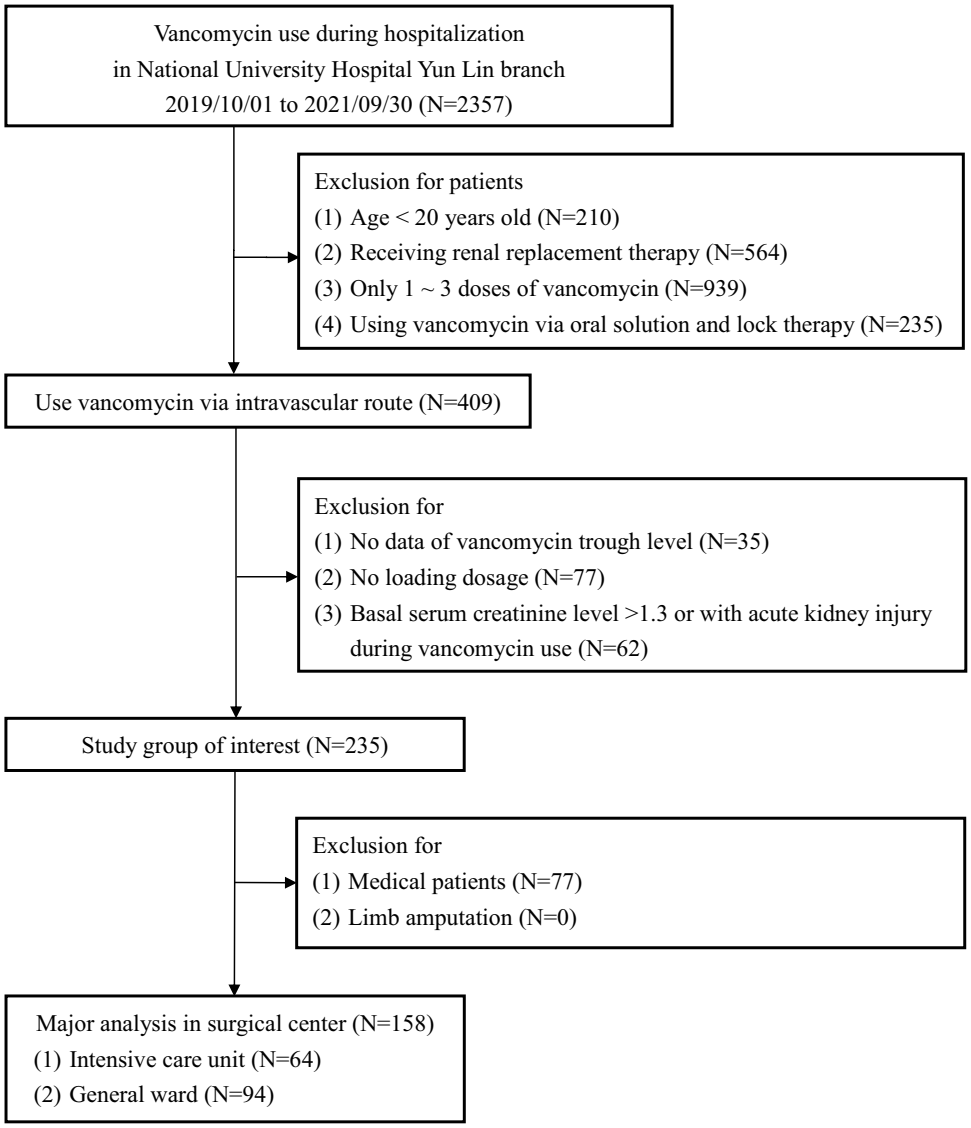

Figure 1 Flowchart of the study population.

Discussion

To the best of our knowledge, this is the first study to confirm that when CKD-EPI eGFR reaches or exceeds 96.5 mL/min/1.73 m^2, surgical ward patients on vancomycin require a dosage higher than 45 mg/kg/day to significantly increase

Table 1 Demographic Characteristics of the Patients

	Total (N=158)
Age, years	61 [20];20–88
Male	107 (67.7)
BMI (kg/m^2)	23.2 [5.3];13.7–42.0
S_{Cr} (mg/dL) at baseline	0.7 [0.3];0.3–1.3
eGFR ($mL/min/1.73m^2$)	97.5 [26];41.1–168.6
Surgery	138 (87.3)
Vancomycin treatment after surgery	116 (73.4)

(*Continued*)

Table 1 (Continued).

	Total (N=158)
Surgery classification	
- Nervous system	61 (38.6)
- Ear, nose and larynx	1 (0.6)
- Heart and major thoracic vessels	3 (1.9)
- Chest wall, pleura, mediastinum, diaphragm, trachea, bronchus and lung	4 (2.5)
- Digestive system and spleen	11 (7.0)
- Musculoskeletal system	56 (35.4)
- Skin	5 (3.2)
ICU admission	64 (40.5)
- Trauma admission	37 (23.4)
Cardiovascular disease	76 (48.1)
Diabetes mellitus, type 2	46 (29.1)
Intracranial hemorrhage	39 (24.8)
Subarachnoid hemorrhage	16 (10.1)
Under treatment of mannitol	29 (18.4)
Vancomycin indication	
Empirical use	85 (53.8)
Wound infection	42 (26.6)
Bacteremia	17 (10.8)
Pneumonia	8 (5.1)
Osteomyelitis	2 (1.3)
Empyema	1 (0.6)
Meningitis	2 (1.3)
Brain abscess	1 (0.6)
Vancomycin loading dose (mg/kg/day)	21.0 [8.0];9.0–37.0
Vancomycin maintenance dose (mg/kg/day)	33.0 [18.5];11.0–71.0
Treatment duration (days)	12 [11];2–53
Days between vancomycin initiation and trough level sampling	3 [1];2–5
Serum trough level, mg/L	14.0 [8.4]; 2.0–44.6
AUC_{24h}, mg/L x hr	446.0 [193];198–997

Note: Data presented as median [interquartile ranges]; minimum-maximum or n (%).
Abbreviations: BMI, body mass index; S_{Cr}, serum creatinine; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; AUC, area under the curve.

Table 2 Comparison of the Demographics and Vancomycin Use Patterns of the ARC and Non-ARC Groups

	ARC (N=85)	Non-ARC (N=73)	P value
Age, years	51 [20];20–88	70 [16];42–87	<0.001*
Male	61 (71.7)	46 (63.0)	0.24
BMI (kg/m^2)	22.7 [4.8];13.7–42.0	24 [5.5];17.2–35.4	0.36
S_{Cr} (mg/dL) at baseline	0.6 [0.2];0.3–0.9	0.9 [0.4];0.5–1.3	0.01*
eGFR ($mL/min/1.73m^2$)	110.3 [19.4];96.6–168.6	83.8 [28];41.1–96.4	<0.001*
Surgery	77 (90.6)	60 (83.6)	0.19
-Nervous system	35 (41.2)	26 (35.6)	0.47
-Ear, nose and larynx	1 (1.2)	0 (0.0)	1.00
-Heart and major thoracic vessels	1 (1.2)	2 (2.7)	1.00
-Chest wall, pleura, mediastinum, diaphragm, trachea, bronchus and lung	4 (4.7)	0 (0.0)	0.13
-Digestive system and spleen	7 (8.2)	4 (5.5)	0.23

(*Continued*)

Table 2 (Continued).

	ARC (N=85)	Non-ARC (N=73)	P value
-Musculoskeletal system	33 (38.8)	23 (31.5)	0.34
-Skin	2 (2.4)	3 (4.1)	0.66
ICU admission	39 (45.9)	25 (34.3)	0.14
Trauma admission	27 (31.8)	10 (13.7)	0.008*
Cardiovascular disease	27 (31.8)	49 (67.1)	< 0.001*
Diabetes mellitus, type 2	19 (22.4)	27 (37.0)	0.04*
Intracranial hemorrhage	23 (27.1)	16 (21.3)	0.46
Subarachnoid hemorrhage	8 (9.4)	8 (11.0)	0.75
Under treatment of mannitol	22 (25.9)	7 (9.6)	0.008*
Vancomycin loading dose (mg/kg/day)	21.0 [7.5];11.0–37.0	20.0 [7.0];9.0–31.0	0.14
Vancomycin maintenance dose (mg/kg/day)	42.0 [20.5];18.0–71.0	28.0 [12.0];11.0–56.0	< 0.001*
Treatment duration (days)	12.0 [10.5];3.0–43.0	12.0 [11.0];2.0–53.0	0.465
Days between vancomycin initiation and trough level sampling	3.0 [0];2.0–5.0	3.0 [1];2.0–5.0	0.090
Serum trough Level, mg/L	11.7 [8.6];2.0–36.3	15.4 [7.0];5.5–44.6	0.001*
AUC_{24h}, mg/L x hr	408 [196];198–934	467 [183];223–997	0.008*

Note: *p < 0.05. Data presented as median [interquartile ranges]; minimum-maximum or n (%).
Abbreviations: ARC, augmented renal clearance; BMI, body mass index, S_{Cr}, serum creatinine; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; AUC, area under the curve.

the likelihood of achieving an AUC/MIC target of >400. Vancomycin is a glycopeptide antibiotic that is primarily used to treat MRSA infections.[4] Because postoperative surgical ward patients often experience wound infections, vancomycin is frequently used empirically to treat MRSA.[21] The PK/PD target for vancomycin is the AUC/MIC ratio, which is currently recommended to be within 400–600 to ensure efficacy and mitigate the risk of nephrotoxicity.[4] Previously, monitoring the trough concentration of vancomycin, which typically ranges from 15 to 20 mg/L, was recommended.[22] However, many studies have indicated that in a large proportion of patients, AUC may exceed 400 even at trough concentrations of 10–15 mg/L,[23] and significant nephrotoxicity occurs more frequently when trough concentrations are maintained at 15–20 mg/L as compared with <15 mg/L.[4]

Low drug concentrations may increase the risk of subsequent bacterial resistance, and ARC is a well-known risk factor for subtherapeutic drug concentrations.[5,24] ARC is clinically defined as a creatinine clearance rate of ≥130 mL/min/1.73 m^2, which often results from high sympathetic nervous system activity under stress, leading to increased cardiac output and

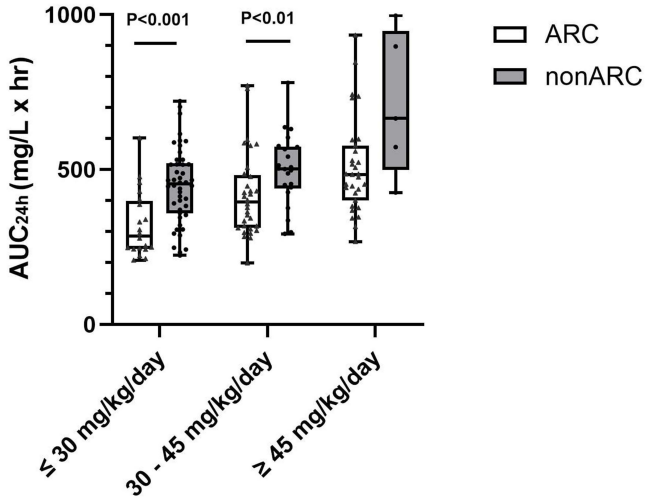

Figure 2 Comparison of the AUC_{24h} values of vancomycin in the ARC and non-ARC groups.
Abbreviations: AUC, area under the curve; ARC, augmented renal clearance.

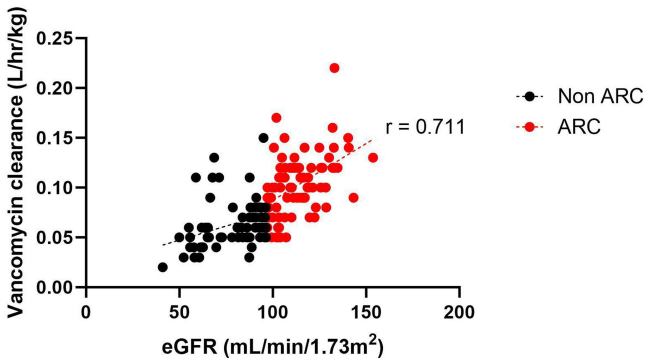

Figure 3 Correlation between vancomycin clearance and CKD-EPI eGFR in the ARC and non-ARC groups.
Abbreviations: eGFR, estimated glomerular filtration rate; ARC, augmented renal clearance.

renal perfusion and thereby increased renal elimination of substances.[11,12,25] High-volume fluid resuscitation or vasopressors may lead to ARC through a similar mechanism.[11,12,25] ARC is primarily observed in critically ill patients and in patients with burns, trauma, and cerebral hemorrhage, and it is also sometimes observed in other conditions such as hematological malignancies.[11,12,25–28] Measuring urine creatinine clearance is regarded as the most accurate method for clinically confirming ARC.[11,12,29] However, this method is associated with delayed information availability, prompting many studies to explore the efficacy of other renal function estimation formulas, such as the CG, MDRD, and CKD-EPI equations, in predicting ARC in various disease states. Declercq et al[17] indicated that the GFR estimated using the CKD-EPI equation and 8-hour urine creatinine levels exhibited the most favorable correlation in non–critically ill patients undergoing abdominal surgery and those hospitalized for trauma. Gijsen et al[15] reported that adopting a CKD-EPI cutoff of 96.5 mL/min/1.73 m^2 enabled the accurate assessment of ARC in critically ill patients. However, whether this cutoff can be extrapolated to surgical ward patients to predict low vancomycin concentrations and AUC/MIC ratios of renally excreted drugs such as vancomycin remains unknown. In this study, we confirmed that, with CKD-EPI eGFR ≥ 96.5 mL/min/1.73 m^2, surgical ward patients who are maintained at a vancomycin dosage of >45 mg/kg/day are significantly likely to achieve an AUC/MIC ratio of >400. This result is consistent with the findings of Sahraei et al,[30] who reported that, in patients with brain trauma and ARC, a dosage of 15 mg/kg q8h (45 mg/kg/day), as compared with 15 mg/kg q12h (30 mg/kg/day), significantly increased the likelihood of achieving an AUC/MIC ratio of >400 (82.14% vs 46.42%).

This study has some limitations. First, this was a retrospective study with a small number of patients, and we primarily focused on the efficacy of the CKD-EPI equation in predicting higher vancomycin dose in surgical ward patients, which may not be generalizable to other patient populations. Although the small sample size of our study, a post-hoc power calculation was conducted using sample sizes of 85 and 73 for each group, a type I error of 0.05, and an effect size of 0.66, which was determined by the mean and standard deviation of each group. The power of the study was 0.98, which is considered acceptable. Second, because vancomycin is typically used empirically, we did not evaluate the relationship between the AUC/MIC ratio and clinical outcomes. Third, because we did not collect data on urine creatinine clearance, we were unable to accurately determine the actual rate of ARC. In patients with CKD-EPI eGFR ≥ 96.5 mL/min/1.73 m^2, the serum levels of vancomycin considerably decrease, indicating a high likelihood of ARC in this group. These findings can serve as a valuable reference for empirical vancomycin dosing through CKD-EPI eGFR. Lastly, while the vancomycin population PK model we employed is based on patients with hematological malignancies, who have been well-documented in previous studies as being at high risk for ARC,[31–33] the most robust evidence would come from developing a PK model specifically designed for a surgical population.

Conclusion

In surgical ward patients, when CKD-EPI eGFR reaches or exceeds 96.5 mL/min/1.73 m^2, the maintenance dose of vancomycin may be increased to >45 mg/kg/day to increase the likelihood of achieving an AUC/MIC ratio of >400.

Subsequent regularly monitoring of blood concentrations and renal function remains necessary to ensure therapeutic efficacy and prevent toxicity.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

There was no conflict of interest in this study.

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