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Individualized Vancomycin Dosing with Therapeutic Drug Monitoring and Pharmacokinetic Consultation Service: A Large-Scale Retrospective Observational Study

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Background: To date, outcome data with a large sample size and data regarding the clinical outcomes of pharmacokinetic-guided (PK) dosing of vancomycin are limited.

Aim: We evaluated the pharmacokinetic and clinical outcomes of a PK-guided dosing advisory program, pharmacokinetic consultation service (PKCS), in vancomycin treatment.

Methods: We investigated vancomycin therapeutic drug monitoring (TDM) and PKCS use through a retrospective review of patients who had serum vancomycin trough concentration data from October 2017 to November 2018. Among these patients, we selected non-critically ill adult patients satisfying our selection criteria to evaluate the effect of PKCS. Target trough attainment rate, time to target attainment, vancomycin-induced nephrotoxicity (VIN), vancomycin treatment failure rate, and duration of vancomycin therapy were compared between patients whose dosing was adjusted according to PKCS (PKCS group), and those whose dose was adjusted at the discretion of the attending physician (non-PKCS group).

Results: A total of 280 patients met the selection criteria for the VIN analysis (PKCS, n=134; non-PKCS, n=146). The incidence of VIN was similar between the two groups (PKCS, n=5; non-PKCS, n=5); however, the target attainment rate was higher in the PKCS group (75% vs 60%, $P = 0.012$). The time to target attainment was similar between the two groups. Further exclusions yielded 112 patients for the clinical outcome evaluation (PKCS, n=51; non-PKCS, n=61). The treatment failure rate was similar, and the duration of vancomycin therapy was longer in the PKCS group (12 vs 8 days, $P = 0.008$).

Conclusion: In non-critically ill patients, an increase in target trough achieved by PKCS did not lead to decreased vancomycin treatment failures, shorter vancomycin treatment, or decreased nephrotoxicity in vancomycin treatment. Considering the excessive amount of effort currently put into vancomycin dosing and monitoring, more selective criteria for individualized pharmacokinetic-guided dosing needs to be applied.

Keywords: vancomycin, pharmacokinetics, dosing, therapeutic drug monitoring, trough concentration, nephrotoxicity

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Introduction

Vancomycin, a glycopeptide antimicrobial agent, plays an important role in the treatment of gram-positive infections,[1] especially as the first-line therapy for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) strains.[2–4] Vancomycin is a time-dependent killing antibiotics that is most effective when

the concentration at the infection site is maintained above the minimum inhibitory concentration (MIC) throughout the dose interval.[5] In the light of accumulated evidences to date, a ratio of area under the curve over 24 hours to MIC determined by broth microdilution (AUC_{24}/MIC_{BMD}) of ≥400 is currently considered the optimal pharmacokinetic/pharmacodynamics (PK/PD) efficacy target.[3,6–9]

Two major concerns exist with vancomycin. One is the emergence of vancomycin-resistant isolates due to failure of vancomycin therapy[10,11] and the other is vancomycin-induced nephrotoxicity (VIN, which is used interchangeably with vancomycin-associated acute kidney injury).

Owing to the narrow therapeutic index, dosing and monitoring of vancomycin have been subject of deliberation over the years.[3,6,12–17] Along with monitoring of drug concentration, individualized (personalized) dosing via PK tools have been suggested as an assisting tool to obtain a more precise PK target.[3,6,9,12,17–29]

However, the evidence for PK-guided dosing is still insufficient.[3,9,19,30] Although an abundant number of studies have evaluated the effectiveness of PK-guided dosing, most of them employed a pre-post intervention study design.[20,27,31–39] Pre-post intervention studies do not have control over other elements that change at the same time as the intervention is implemented. Therefore, the changes in the outcome during the study period cannot be fully attributed to the evaluated intervention.[40–42] Among the limited number of studies employing retrospective observational study design which could confer temporality, the maximum number of sample size is only 100 patients[25] and among these retrospective studies, one that evaluated a clinical outcome with the largest sample size included only 43 patients[43] that type 2 error could not be excluded.

In the year 2020, a revision was made to the 2009 consensus guidelines with respect to serious MRSA infections.[9] Based on study results showing increased VIN without improved outcomes via targeting a serum trough concentration of 15–20 μg/mL, maintaining an AUC_{24}/MIC of 400–600 via AUC-monitoring was suggested to minimize nephrotoxicity with maximum clinical effectiveness in serious MRSA infections.[9,30,44–50]

However, the evidence for this recommendation was only A-II, which means that the evidence for the recommendation is good in quality, but is based only on retrospective studies without any randomized controlled trials.[9,51] Although monitoring and targeting AUC has recently been associated with improved outcomes in MRSA infections,[24,48,52–54] the prerequisites required to implement AUC monitoring, such as training and education of the related medical professionals (ie, pharmacists, physicians, phlebotomists and nursing staff) and installation of third-party pharmacokinetic calculation or Bayesian software, makes it impractical for clinical use at most hospitals at this time.[55–58] In contrast to the considerable requirements for AUC monitoring, serum trough concentration is easily applicable on account of readily available serum vancomycin concentration assays, and many medical centers still monitor trough concentration.[58]

Considering the relatively weak quality of evidence compared to the effort that laboratories would need to invest in the implementation of AUC monitoring, and the subsequent prevalence of trough monitoring over AUC, we evaluated the pharmacokinetic and clinical outcomes of trough-based PK-guided dosing despite the newly revised guidelines. Moreover, we investigated the use of vancomycin TDM and PK-guided dose adjustment in a real clinical setting with a large sample size. Through this large-scale retrospective study, evaluating both pharmacokinetic and clinical outcomes, we expect to add to the growing body of literature on the evidence for PK-guided dosing and help to establish a patient selection criteria for the application of PK-guided dosing.

Methods

Description of the Pharmacokinetic Consultation Service

In our institution, attending physicians can request a "pharmacokinetic consultation service" (PKCS), which is a pharmacokinetic dose adjustment advisory program based on therapeutic drug monitoring (TDM) provided by an institutional consultation team. In this study, we used the term TDM as the measurement of a specific drug level for optimal drug use. Upon receiving a request for PKCS, patient information is collected through communication with the attending physician and comprehensive review of electronic medical records regarding clinical information, microbial information, drug regimen, actual drug administration history and laboratory data. By putting this information into the PK equation or Bayesian software program, Abbottbase® Pharmacokinetic Systems v 1.10 (Abbott laboratories, Abbott Park, IL, USA) and MwPharm++ (Mediware, Praha, Czech Republic), the clinical pharmacist or laboratory medicine doctor provides

the best possible dosing and monitoring regimen to the physician.

In contrast, in patients for whom PKCS has not been prescribed, the dosing and monitoring of vancomycin are determined at the discretion of the physician.

Study Design and Population

This was a retrospective study conducted among hospitalized patients at Samsung Medical Center (Seoul, Korea), a 2000-bed academic medical center, from November 2017 to October 2018. This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: SMC 2017–12-038-004). To minimize the risk of harm to subjects resulting from breach of confidentiality, precautions were taken to limit record review to specific, de-identified data. The need for written informed consent was waived due to the retrospective nature of the study.

Before evaluation of PKCS, we investigated utilization of vancomycin therapeutic drug monitoring (TDM) in our institution. We retrospectively analyzed 12,846 serum vancomycin trough concentration results obtained from 2412 patients using the following data: age, sex, hospitalization status (ie, hospitalized or outpatient), department to which the patient was admitted, and whether the patient received PKCS.

The study design and patient selection for evaluation of PKCS are summarized in Figure 1. A total of 280 patients were enrolled in the evaluation of incidence of VIN. Patients were included if they were >18 years old, hospitalized in the general ward of the surgery department, received vancomycin for more than 48 h, met the criteria for vancomycin TDM according to the 2009 vancomycin TDM guidelines (ie, patients receiving aggressive dosing targeted to produce sustained trough drug concentration of 15–20 μg/mL, receiving concurrent nephrotoxic agents, having unstable renal function, or receiving prolonged course of therapy longer than three to five days)[6] and with available steady-state serum vancomycin trough concentration data. We excluded patients with a history of admission to the critical care unit during vancomycin treatment or who were hospitalized in the neurosurgery department. We also excluded patients who had insufficient data regarding clinical indications for vancomycin therapy, vancomycin dose regimen, or serum creatinine level during vancomycin treatment. Patients whose

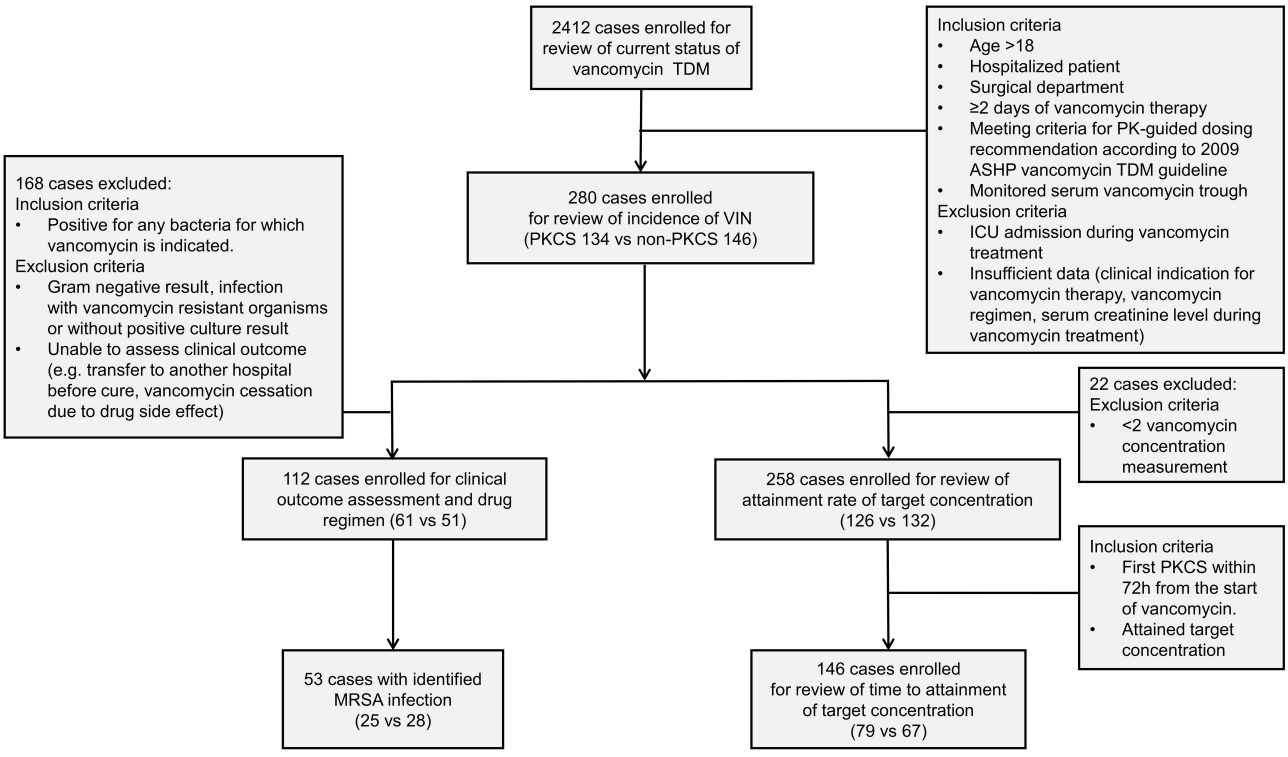


Figure 1 Study design and patient population.

Abbreviations: TDM, therapeutic drug monitoring; PK, pharmacokinetic; ASHP, American Society of Health-System Pharmacists; ICU, intensive care unit; VIN, vancomycin induced nephrotoxicity; PKCS, pharmacokinetic consultation service; MRSA, methicillin resistant *Staphylococcus aureus*.

vancomycin dosing was managed by a primary physician without PKCS served as controls (non-PKCS group, n=146), and patients whose dosing regimen was managed following the PKCS recommendations were stratified into the PKCS group (n=134).

Among the 280 patients, we selected 258 patients with at least two steady-state serum trough concentrations and compared the target concentration attainment rate between the control (non-PKCS, n=132) and intervention (PKCS, n=126) groups. Of these 258 patients, the time to initial target trough from the start of vancomycin therapy was compared between those who both received PKCS within the first 72 h from the start of vancomycin therapy and succeeded in attaining target trough (n=67) and the control group patients who attained target trough (n=79).

Clinical outcome assessment was performed in 112 patients with culture-confirmed infection of any bacteria for which vancomycin was indicated (non-PKCS, n=61; PKCS, n=51). Those with gram-negative results, without a positive culture result or infected with vancomycin-resistant organisms were excluded. We also excluded patients whose vancomycin treatment outcome was not assessable, such as patients who ceased vancomycin therapy due to side effects or who were transferred to another hospital before the treatment outcome could be assessed. We also examined clinical outcomes in a subset of patients with culture-confirmed MRSA infection (non-PKCS, n=25; PKCS, n=28).

Data Collection

Following data were collected from the electronic medical records of eligible patients: age, sex, weight, height, diagnosis for vancomycin therapy, comorbidities, hospitalization department, site of infection, target trough range, concomitant nephrotoxic agents, incidence of VIN, culture results, MIC for vancomycin in MRSA infection, duration of vancomycin therapy, vancomycin drug regimen (ie, dose, dose frequency, dose duration, route of administration), actual drug administration history, serum vancomycin concentration with sampling time, serum creatinine, estimated glomerular filtration rate (GFR), white blood cell (WBC) count, C-reactive protein (CRP) from two days before and after the vancomycin therapy period, frequency of trough measurement, frequency of drug regimen change, and clinical outcomes. Diagnoses including comorbidities, site of infection and clinical outcome were identified through physician's notes. The baseline and final serum creatinine was determined as the first and the last serum creatinine value and recorded between 24 h before the initiation of vancomycin therapy and 48 h after the completion of vancomycin therapy. The baseline and final estimated GFR was calculated with baseline and final serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[59] For each patient, initial CRP and WBC count was recorded, which was defined as the CRP and WBC count value recorded within 24 h from the start of the vancomycin therapy. Concomitant nephrotoxic agents included aminoglycosides, amphotericin, piperacillin-tazobactam, vasopressor, loop diuretics, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and acyclovir.[60]

Serum Vancomycin Concentration

The serum vancomycin concentration was measured with a kinetic interaction of microparticles in solution (KIMS) immunoassay on Roche Cobas 8000 c702 analyzer (Roche, Basel, Switzerland). In this study, we only included steady-state vancomycin trough concentration. The policy of our institutions advises vancomycin trough concentration be obtained just prior to the 3rd or 4th dose of the new dose regimen as the steady-state trough concentration with normal renal function.

In addition to analyzing every concentration, in patients with at least two concentrations measured, we also selected each patient's "maximum" and "final" concentration. The "maximum" concentration was defined as the highest trough concentration measured in each patient during vancomycin treatment while the "final" concentration was defined as the ultimate trough concentration measured in each patient.

Target Trough Range

The target range of trough concentration was decided according to the site and the causal microorganism of the infection by the attending physician, pharmacist or laboratory medicine doctor (with or without consultation to infectious disease specialist). For suspected or definite bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia by *Staphylococcus aureus* (*S. aureus*), the target serum trough concentration was 15–20 μg/mL. For suspected or definite infections of sites other than the aforementioned sites, and pathogens other than *S. aureus*, the target concentration was 10–15 μg/mL.[6] Concentrations below, within, and exceeding the target range were categorized as subtherapeutic, therapeutic, and supratherapeutic, respectively.

Microbiological Data

The patient's culture result was investigated. For positive culture results, identified microorganisms were recorded. The microorganism was identified by matrix-assisted laser desorption ionization-time of flights mass spectrometry using the VITEK-MS (bioMérieux, Marcy l'Etoile, France). For MRSA infection, the MIC for vancomycin was determined via VITEK 2 System (bioMérieux, Marcy l'Etoile, France), with MRSA isolates demonstrating MICs above 4 mg/L being subjected to confirmation with an E-test. The usual turn around time for identification and antimicrobial susceptibility testing of positive blood culture was 24–72 h depending on the growth rate of the tested microorganism.

Comorbidities

The patient's comorbidities were investigated through the physician's note. Among the comorbidities, we recorded the presence of malignancy under treatment and diabetes mellitus. Also, if present, concurrently active diseases that could affect the patient's condition were recorded and classified into cardiovascular, pulmonary, central nervous system, and gastrointestinal disease.

Vancomycin Treatment Outcome

Vancomycin treatment outcome was classified into treatment failure or success. Treatment failure was defined as the development of VIN, the need to add or change therapy to another drug with a similar spectrum of activity (daptomycin, linezolid, or tigecycline), or the return of signs or symptoms of the original infection within 72 h after successful therapy. Treatment success was defined as resolution or improvement of the original signs or symptoms of infection and cessation of vancomycin.

Nephrotoxicity and Outcome Assessment

For nephrotoxicity assessment, the development of VIN was evaluated. VIN was defined as a minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or a ≥50% increase from baseline, whichever is greater) after the start of vancomycin therapy with the exclusion of any other possible documented cause for acute kidney injury.[6,61]

The primary outcome was the attainment of target vancomycin trough concentrations, and the time to the initial target trough from the start of vancomycin treatment. In the PKCS group, only those who received PKCS and changed drug regimen according to PKCS within 72 h from the start of vancomycin treatment were included for the evaluation of the time to first target trough. The secondary outcome included vancomycin treatment outcome, duration of vancomycin therapy, daily dose of vancomycin, frequency of vancomycin concentration measurement and regimen change.

Statistical Analysis

All statistical analyses were performed using Medcalc® version 77.5.1.0 (MedCalc Software Ltd., Ostend, Belgium) or IBM SPSS® Statistics version 25 (IBM Corp., Armonk, NY, USA). For intergroup comparison between PKCS and non-PKCS group, all continuous data were checked for normality. After identifying the non-normal distribution of the included data, they were reported as the median and interquartile range (IQR) and were compared using the Mann–Whitney Rank-sum test. Data showing normal distribution were reported in mean with range, and were compared using the independent samples *t*-test. A Chi-square and Fisher's exact test were used to compare two categorical data points. Univariate and multiple logistic regression analyses were performed to evaluate the relationship between heterogeneous covariates with the incidence of VIN, the attainment of the target trough, and vancomycin treatment failure. Initially, we performed the univariate logistic regression analysis on the following parameters to screen covariate for multiple logistic regression analysis: group (PKCS or non-PKCS), age, sex, body mass index (BMI), comorbidities (malignancy, diabetes), target trough, site of infection, culture result (positive or negative), use and type of concomitant nephrotoxic agent, baseline serum creatinine level and estimated GFR, initial WBC count and CRP level during vancomycin therapy, duration of vancomycin therapy, daily dose of vancomycin, and vancomycin concentration (mean, maximum, and final vancomycin concentration). Subsequently, multiple logistic regression analysis was performed with the covariates that demonstrated a significant effect ($P < 0.20$) in univariate logistic regression. When there was highly inter-related covariates among the covariates selected from univariate logistic regression (eg, mean vancomycin concentration and maximum vancomycin concentration), we chose only one among the inter-related covariates to avoid multicollinearity. For all analyses except for univariate logistic

regression, a P value < 0.05 was considered to be statistically significant.

Results

Vancomycin TDM

We reviewed a total of 2412 patients who received vancomycin TDM. Patient characteristics are summarized in Table 1. Of these patients, 1473 (61.1%) were male and 2411 (99.9%) were hospitalized. The median age was 63 years old (IQR 49–72 years). TDM was mostly requested from the surgical (27.6%), hemato-oncology (21.9%), and critical care medicine department (12.1%). In total, 528 patients (21.9%) received PKCS. There was no significant demographic difference between patients who received PKCS (n = 528) and those that did not (n = 1884). PKCS was requested the most by surgical departments (41.9%). In contrast, vancomycin dosing was managed more without PKCS in the hemato-oncology and critical care medicine department. Median vancomycin concentration was 14.7 μg/mL (IQR 10.9–18.3 μg/mL and the frequency of concentration measurement was median 3 times (IQR 2–7 times). The proportion of therapeutic, subtherapeutic and supratherapeutic concentrations was 63.6%, 20.3%, and 16.1%, respectively.

Nephrotoxicity Assessment

For the evaluation of nephrotoxicity development, 280 patients (non-PKCS, n = 146; PKCS, n = 134), were enrolled. Patient characteristics and results of comparison are summarized in Table 2. There was no significant difference in the incidence of VIN (non-PKCS, 3% (5/146); non-PKCS, 6% (8/134); P = 0.398). No significant difference in baseline characteristics were observed except in BMI (24 kg/m^2 vs 20 kg/m^2, P < 0.001) and in the proportion of obese patients (BMI >30kg/m^2, 10% vs 1%, P = 0.002). The non-PKCS group had a higher proportion of patients who used vancomycin for ear, nose and throat infection (15% vs 5%, P = 0.007), and for surgical prophylaxis (5% vs 1%, P = 0.037). Meanwhile, the PKCS group had a higher proportion of patients with methicillin-resistant coagulase negative *Staphylococcus* (MRCNS) infections (5% vs 13%, P = 0.011), concurrent nephrotoxic agent use (49% vs 63%, P = 0.024), and a longer duration of vancomycin therapy (6 vs 9 days, P < 0.001). However, none of the above variables were associated with a significant odds ratio (OR) for the development of VIN in logistic regression analysis (Table 3).

Table 1 Characteristics and Vancomycin Trough Concentration in Patients Who Underwent Vancomycin Therapeutic Drug Monitoring

Characteristics	Total	Without PKCS	With PKCS	*P* value
Total number of patients, n	2412	1884 (78.1%)	528 (21.9%)	
Total no. of vancomycin concentration measurements, n	12846	9702 (75.5%)	3144 (24.5%)	
Age, median (IQR), years	61 (46–71)	60 (46–71)	63 (49–72)	**0.022**
Age < 18 years, n (%)	264 (10.9%)	208 (11.0%)	56 (10.6%)	0.778
Male, n (%)	1473 (61.1%)	1153 (61.2%)	320 (60.6%)	0.805
Hospitalized patient, n (%)	2411 (99.9%)			
Department, n (%)				
Surgical department[a]	666 (27.6%)	445 (23.6%)	221 (41.9%)	
Hemato-oncology	529 (21.9%)	481 (25.5%)	48 (9.1%)	
Critical care medicine	292 (12.1%)	228 (12.1%)	64 (12.1%)	
Pediatrics	206 (8.5%)	167 (8.9%)	39 (7.4%)	
Others	719 (29.8%)	563 (29.9%)	156 (29.5%)	
No. of measurements per patient, median (IQR), n	3 (2–7)	3 (2–6)	4 (2–7)	**<0.001**
Vancomycin concentration, median (IQR), μg/mL	14.7 (10.9–18.3)	14.5 (10.8–18.1)	15.2 (11.3–18.6)	**<0.001**
Subtherapeutic, n (%)	2610 (20.3%)	2046 (21.1%)	564 (17.9%)	**<0.001**
Therapeutic, n (%)	8173 (63.6%)	6144 (63.3%)	2029 (64.5%)	0.229
Supratherapeutic, n (%)	2063 (16.1%)	1512 (15.6%)	551 (17.5%)	**0.009**

Notes: [a]Surgical department includes general surgery, neurosurgery, plastic surgery and thoracic surgery. Significant values are indicated in bold.
Abbreviations: PKCS, pharmacokinetic consultation service; IQR, interquartile range.

Table 2 Characteristics of the Patients Enrolled for VIN Assessment

	Non-PKCS (n=146)	% or IQR	PKCS (n=134)	% or IQR	*P* value
Incidence of VIN, n (%)	5	3%	8	6%	0.398
Duration of vancomycin therapy, days	6	4–8	9	5–15	**<0.001**
Daily dose of vancomycin[a], mg/kg/day	33	27–41	34	26–40	0.724
Male, n (%)	76	52%	83	62%	0.095
Age, years	63	54–72	67	54–73	0.212
No. of races other than East Asian, n (%)	1	1%	0	0%	N/A
Weight, kg	64	54–72	61	54–67	0.169
BMI[a], kg/m^2	24	21–27	20	18–22	**<0.001**
Obesity (BMI>30kg/m^2), n (%)	15	10%	2	1%	**0.002**
Target trough					
10–15 μg/mL, n (%)	81	55%	64	48%	0.197
15–20 μg/mL, n (%)	65	45%	70	52%	
Renal Function					
Serum creatinine, mg/dL	0.78	0.61–0.96	0.75	0.56–0.98	0.348
Baseline eGFR, mL/min/1.73 m^2	90	74–104	95	77–105	0.41
≥90	72	49%	81	60%	0.062
60–89	52	36%	35	26%	0.086
<60	22	15%	18	13%	0.696
Renal replacement therapy, n (%)	11	8%	7	5%	0.431
Final eGFR, mL/min/1.73 m^2	93	73–107	90	67–104	0.698
Co-morbidities					
Malignancy, n (%)	52	36%	41	31%	0.373
Cardiovascular, n (%)	20	14%	26	19%	0.198
Pulmonary, n (%)	5	3%	1	1%	0.216
Central nervous system, n (%)	2	1%	4	3%	0.431
Gastrointestinal, n (%)	13	9%	9	7%	0.497
Diabetes, n (%)	37	25%	24	18%	0.132
Site of Infection					
Respiratory, n (%)	9	6%	15	11%	0.133
Blood stream, n (%)	24	16%	15	11%	0.065
Skin and soft tissue, n (%)	27	18%	39	29%	0.367
Central nervous system, n (%)	7	5%	9	7%	0.489
Bone/Joint, n (%)	25	17%	29	22%	0.338
Intra-abdominal, n (%)	22	15%	15	11%	0.339
Ear, nose and throat, n (%)	22	15%	7	5%	**0.007**
Urinary tract, n (%)	2	1%	4	3%	0.431
Surgical prophylaxis, n (%)	8	5%	1	1%	**0.037**
Positive culture result[b]					
MRSA, n (%)	28	19%	30	22%	0.417
MRCNS, n (%)	7	5%	18	13%	**0.011**
MSSA, n (%)	3	2%	2	1%	1
Enterococcus sp., n (%)	12	8%	14	10%	0.521
Other gram positives[c], n(%)	4	3%	9	7%	0.156
Empirical use	27	18%	20	15%	0.33
Concurrent nephrotoxic agents[d]	72	49%	84	63%	**0.024**
Piperacillin/tazobactam, n (%)	42	29%	52	39%	0.758
Furosemide, n (%)	36	25%	40	30%	0.329

(*Continued*)

Table 2 (Continued).

	Non-PKCS (n=146)	% or IQR	PKCS (n=134)	% or IQR	*P* value
ACE inhibitor or ARBs, n (%)	6	4%	3	2%	0.504
Aminoglycosides, n (%)	2	1%	6	4%	0.158
Vasopressin, n (%)	2	1%	1	1%	1
Initial CRP[e], mg/dL	3.8 (n=130)	1.3–9.0	5.7 (n=132)	1.7–10.4	0.105
Initial WBC count[e], /mL	7.3 (n=134)	5.3–10.3	8 (n=133)	5.9–11.3	0.15

Notes: [a]All of the values were described in the median with interquartile range (IQR) given their non-normal distribution except for daily dose and BMI which followed normal distribution and was described in mean with range and compared with an independent sample *t*-test. [b]Infection with two microorganisms indicated for vancomycin existed (11 cases in PKCS group). [c]Other gram positives include *Streptococcus* species, *Corynebacterium* species, *Propionibacterium acnes*, and *Bacillus cereus*. [d]Patients using two or more concurrent nephrotoxic agents existed (19 cases in PKCS group, 19 cases in non-PKCS group). [e]Patients without the result of CRP and WBC count existed. Significant values are indicated in bold.

Abbreviations: VIN, vancomycin induced nephrotoxicity; PKCS, pharmacokinetic consultation service; IQR, interquartile range; BMI, body mass index; eGFR, estimated glomerular filtration rate; MRSA, methicillin resistant *Staphylococcus aureus*; MRCNS, methicillin resistant coagulase negative *Staphylococcus*; MSSA, methicillin susceptible *Staphylococcus aureus*; ACE inhibitor, Angiotensin-converting enzyme inhibitor; ARBs, Angiotensin II receptor blockers; CRP, C-reactive protein; WBC, white blood cell.

Primary Outcome – Attainment of Target Trough Concentration

Among the 280 patients who received vancomycin treatment for at least two days, 258 patients who had at least two trough concentration measurements were selected for the evaluation the target trough attainment evaluation (non-PKCS, n = 132; PKCS, n = 126). Baseline characteristics and analysis of the trough concentrations are summarized in Table 4. Baseline characteristics were similar with the patients enrolled for VIN assessment except for CRP, which was significantly higher in the PKCS group (3.5 vs 5.8, $P = 0.04$). The target attainment rate was also significantly higher in the PKCS group (60% vs 75%, $P = 0.012$). Likewise, logistic regression analysis demonstrated that receiving PKCS significantly increased the odds for target trough attainment (OR=1.80, 95% CI = 1.05–3.11, $P = 0.034$, Table 5) and the proportion of the final trough concentration in target range was significantly higher in the PKCS group (32% vs 44%, $P = 0.005$). For the comparison of the time to target attainment, 67 patients from the non-PKCS group who achieved target trough were enrolled along with 79 patients from the PKCS group who received PKCS and changed drug regimen according to PKCS within 72 h from the start of vancomycin treatment and achieved target trough. The time to initial target trough and target trough attainment rate was similar between the two groups (Figure 2). Each patient's mean and maximum trough concentration was significantly higher in the PKCS group (mean, 14.8 vs 15.5, $P = 0.037$; maximum, 18.7 vs 20.9, $P = 0.001$). The proportion of subtherapeutic concentrations was significantly higher in the non-PKCS group (34% vs 27%, $P = 0.004$), and the proportion of therapeutic concentration was significantly higher in the PKCS group (33% vs 39%, $P = 0.028$). Maximum trough in the supratherapeutic range was significantly higher in the PKCS group (52% vs 68%, $P = 0.009$).

Secondary Outcome – Clinical Outcome

Sixty-one patients from the PKCS group and 51 patients from the non-PKCS group who had a positive culture result for any bacteria for which vancomycin was indicated were enrolled for the assessment of clinical outcome. A comparison of patient characteristics and the clinical outcome are summarized in Table 6. Patient characteristics were similar to those of patients enrolled for VIN assessment. No significant difference in treatment failure rate was observed between the two groups (non-PKCS, 12% (6/51); non-PKCS, 10% (6/61); $P = 0.742$). In logistic regression analysis (Table 7), the time to target attainment from the start of vancomycin therapy demonstrated a significant OR for treatment failure (OR = 0.64, 95% confidence interval, 0.50–0.85, $P = 0.002$), which is in line with a previous report.[32] Duration of vancomycin therapy was longer in the PKCS group (7 vs 12 days, $P = 0.008$), which was observed in the patient group enrolled for VIN and target trough attainment. In the logistic regression analysis for VIN with this population, PKCS failed to show a significant OR.

For the MRSA subset, 28 and 25 patients were enrolled from PKCS and non-PKCS group, respectively. Likewise, there was no significant difference in the treatment failure rate (Table 8). Although the time to initial target trough was significantly shorter in the PKCS group (3.9 vs 2.3 days, $P = 0.015$), PKCS did not demonstrate a significant OR for time to initial target trough in logistic regression ($P = 1.0$). The proportion of patients with MIC of 1 for vancomycin in identified MRSA was significantly higher

Table 3 Logistic Regression Analysis for Vancomycin Induced Nephrotoxicity

Covariate	Univariate		Multiple	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Group (PKCS)	1.79 (0.57–5.62)	0.318		
Duration of vancomycin therapy (day)	1.01 (0.65–1.07)	0.864		
Daily dose of vancomycin	1.00 (0.96–1.04)	0.94		
Male	**0.32 (0.10–1.07)**	**0.064**	0.327 (0.10–1.11)	0.072
Age	1.01 (0.96–1.05)	0.782		
BMI	0.96 (0.83–1.11)	0.569		
Target trough (15–20 μg/mL)	0.66 (0.21–2.07)	0.474		
Baseline eGFR	1.01 (0.99–1.04)	0.319		
Comorbidities				
Malignancy	0.89 (0.27–2.97)	0.848		
Diabetes	0.64 (0.14–2.97)	0.57		
Site of infection				
Respiratory	2.03 (0.42–9.72)	0.378		
Skin and soft tissue	**2.96 (0.96–9.13)**	**0.06**	2.55 (0.81–8.08)	0.111
Central nervous system	1.4 (0.17–11.50)	0.754		
Bone/Joint	0.34 (0.04–2.65)	0.301		
Positive Culture result				
MRSA	0.97 (0.21–4.55)	0.973		
MRCNS	**3.34 (0.86–13.0)**	**0.083**	2.95 (0.72–12.04)	0.131
Initial CRP	0.98 (0.88–1.07)	0.611		
Initial WBC count	0.93 (0.80–1.09)	0.369		
Concurrent nephrotoxic agent	1.29 (0.41–4.04)	0.666		
Piperacillin/tazobactam	0.87 (0.26–2.92)	0.827		
Furosemide	1.73 (0.55–5.45)	0.353		

Note: Significant values are indicated in bold.
Abbreviations: OR, odds ratio; CI, confidence interval; PKCS, pharmacokinetic consultation service; BMI, body mass index; eGFR, estimated glomerular filtration rate; MRSA, methicillin resistant Staphylococcus aureus; MRCNS, methicillin resistant coagulase negative *Staphylococcus*; CRP, C-reactive protein; WBC, white blood cell.

in the PKCS group (24% vs 57%, $P = 0.015$), whereas, with MIC less than or equal to 0.5 for vancomycin was higher in the non-PKCS group, albeit it was not statistically significant (68% vs 43%, $P = 0.114$).

Duration of Vancomycin Therapy

The duration of vancomycin therapy was significantly longer in the PKCS group regardless of the patient population (patient population for review of VIN, target attainment rate, clinical outcome assessment, and population with MRSA infection). In order to clarify whether the longer duration of vancomycin was a result of PKCS rather than a result of the patient's baseline clinical characteristics, we compared the duration of vancomycin therapy between the two groups categorized by the patient's baseline characteristics (Table 9). The results showed that patients with bone and joint infection demonstrated a longer duration of vancomycin therapy (7.0 vs 8.5 days, $P = 0.006$), in contrast, patients with blood stream infection demonstrated a shorter duration of vancomycin therapy (7.0 vs 4.5, $P < 0.001$). In the PKCS group, although not statistically significant, the proportion of patients with bone and joint infection was higher (17% vs 22%, $P = 0.338$), however, the proportion of patients with blood stream infection was lower (16% vs 11%, $P = 0.065$). Thus, it could be assumed that the integration of the difference in the duration of vancomycin among infection sites, and the difference in the proportion of the site of infection may have resulted in a longer duration of vancomycin therapy in the PKCS group.

Discussion

Given the narrow therapeutic index with critical side effects at both subtherapeutic and supratherapeutic level,

Table 4 Target Trough Attainment and Baseline Characteristics of Enrolled Patient

	Non-PKCS (n=132)	% or IQR	PKCS (n=126)	% or IQR	*P* value
Target trough attainment rate, n (%)	79	60%	94	75%	**0.012**
Time to initial target trough[a], days	3.6	2.5–5.2	4.2*	2.3–5.8	0.43
Total trough concentration, μg/mL	15.3	11.5–18.3	16.2	12.8–19.2	**0.001**
Subtherapeutic, n (%)	206	34%	261	27%	**0.004**
Therapeutic, n (%)	201	33%	371	39%	**0.028**
Supratherapeutic, n (%)	199	33%	328	34%	0.588
Mean trough[b], μg/mL	14.8	8.21–22.8	15.5	8.7–24.4	**0.037**
Subtherapeutic, n (%)	51	39%	39	31%	0.196
Therapeutic, n (%)	44	33%	55	44%	0.088
Supratherapeutic, n (%)	37	28%	32	25%	0.633
Maximum trough, μg/mL	18.7	16.7–21.4	20.9	17.1–24.5	**0.001**
Subtherapeutic, n (%)	**31**	**23%**	15	12%	**0.015**
Therapeutic, n (%)	32	24%	25	20%	0.394
Supratherapeutic, n (%)	69	52%	**86**	**68%**	**0.009**
Final trough, μg/mL	16.5	13.6–18.3	16.7	13.4–19.1	0.412
Subtherapeutic, n (%)	41	31%	28	22%	0.109
Therapeutic, n (%)	42	32%	55	44%	**0.005**
Supratherapeutic, n (%)	49	37%	43	34%	0.616
Patient characteristics					
Male, n (%)	70	53%	77	61%	0.21
Age, years	65	55–74	67	55–72	0.271
BMI (kg/m^2)	24	22–27	19	18–23	**<0.001**
Target trough 15–20 mg/L, n (%)	59	45%	66	52%	0.217
Baseline eGFR, mL/min/1.73 m^2	87	74–101	93	81–107	0.398
Concurrent nephrotoxic agent use[c], n (%)	63	48%	77	61%	**0.031**
Initial CRP[d]	3.5	1.1–8.7	5.8	1.7–10.4	**0.04**
Initial WBC count[d]	7.1	5.1–10.0	8	5.9–11.3	0.088
Duration of vancomycin therapy, days	8	6–11	11	7–17	**<0.001**
Daily dose of vancomycin, mg/kg/day	34	28–40	33	26–41	0.61
Incidence of VIN, n (%)	7	5%	8	6%	0.72

Notes: [a]Time to target attainment was compared between PKCS group patients who received their first PKCS within 72 h from the start of vancomycin therapy and achieved target trough (n=79) and non-PKCS group patients who achieved target trough (n=67). [b]Since mean trough concentration followed a normal distribution, it was described in mean with range and compared via independent sample *t*-test. [c]Patients using two or more concurrent nephrotoxic agents existed (19 cases in PKCS group, 18 cases in non-PKCS group). [d]Patients without the result of CRP and WBC count existed. Significant values are indicated in bold.

Abbreviations: PKCS, pharmacokinetic consultation service; IQR, interquartile range; BMI, body mass index; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white blood cell; VIN, vancomycin induced nephrotoxicity.

individualized dosing using PK tools have been suggested as assisting tools to increase the achievement of the pharmacokinetic target.[3,6,9] However, the evidence for the clinical effectiveness of PK-guided dosing was insufficient.[6,9,19] Our study investigated the utilization of vancomycin TDM and trough-based PK-guided dose adjustment, PKCS, in a real clinical setting with large-scale data and evaluated the pharmacokinetic and clinical effects of PKCS in vancomycin treatment among non-critically ill patients. The result showed that 22% of patients who underwent vancomycin TDM underwent PKCS. PKCS resulted in increased target trough concentration attainment; however, it did not lead to improvement in clinical outcomes or safety of vancomycin treatment.

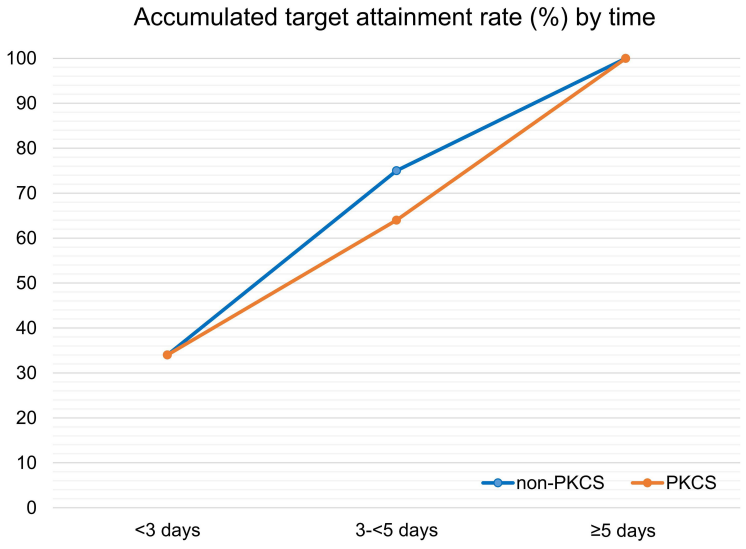
A number of studies have assessed the outcome of individualized dosing guided by PK tools, both in trough-based and AUC-based monitoring.[18,20,22,24,25,28,31–33,35,37–39,43,48,52–54,62–65] Through literature review of 22

Table 5 Logistic Regression Analysis for Target Trough Attainment

Covariate	Univariate		Multiple	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Group (PKCS)	**1.97 (1.16–3.35)**	**0.012**	**1.80 (1.05–3.11)**	**0.034**
Duration of vancomycin therapy	1.22 (1.13–1.32)	**<0.001**		
BMI	0.99 (0.93–1.05)	0.71		
Target trough (15–20 μg/mL)	0.82 (0.49–1.38)	0.455		
Baseline eGFR	1.00 (0.99–1.01)	0.835		
Concurrent nephrotoxic agent use	1.78 (1.05–3.00)	**0.032**	1.65 (0.97–2.82)	0.064
Initial CRP	1.01 (0.97–1.06)	0.556		
Initial WBC	1.01 (0.96–1.07)	0.654		

Note: Significant values are indicated in bold.
Abbreviations: OR, odds ratio; CI, confidence interval; PKCS, pharmacokinetic consultation service; BMI, body mass index; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; WBC, white blood cell.

studies, we found 11 studies evaluating AUC-based dosing,[18,22,24,28,48,52–54,62–64] and the other 11 studies evaluating trough-based PK-guided dosing.[20,25,31–33,35,37–39,43,65] Characteristics of the studies evaluating trough-based PK-guided dosing are summarized in Supplementary Table 1. Among these studies, eight employed pre-post intervention design,[20,31–33,35,37–39] six compared clinical outcome,[20,32,35,37,39,43] and only four involved more than 200 patients.[20,32,35,38] All of the studies that evaluated target attainment rate or the time to initial trough target demonstrated improved outcome in intervention group. Three out of the five studies that evaluated incidence of nephrotoxicity, revealed similar incidence of nephrotoxicity between the intervention,[32,35,38] and one out of the five studies revealed even higher nephrotoxicity rate in the intervention group.[43] Four out of six studies that evaluated clinical outcome,



Time to target attainment	<3 days	3-<5 days	≥5 days
Non-PKCS (n= 79)	27 (34%)	32 (41%)	20 (25%)
PKCS (n= 67)	23 (34%)	20 (30%)	24 (36%)
P value	0.985	0.18	0.168

Figure 2 Cumulative percentage of target trough attainment by time. Percentage of the patients who attained target trough was determined at three time periods (<3 days, 3–<5days, and ≥5days).
Abbreviation: PKCS, pharmacokinetic consultation service.

Table 6 Characteristics of Patients Enrolled for Clinical Outcome Assessment

	Non-PKCS (n=51)	% or IQR	PKCS (n=61)	% or IQR	*P* value
Treatment failure rate, n (%)	6	12%	6	10%	0.742
Duration of vancomycin therapy, days	7	5–12	12	8–17	**0.008**
Daily dose of vancomycin[a], mg/kg/day	33	28–38	30	20–38	0.569
Incidence of VIN, n (%)	2	4%	5	8%	0.452
Target trough attainment rate, n (%)	37	73%	48	79%	0.449
Time to initial target trough[b], days	3.7	2.9–5.2	3.9	2.3–6.4	0.965
No. of trough measurement per week	4.2	3.5–5.3	3.9	3.3–4.9	0.205
No. of dose adjustment per week	1.2	0.0–1.8	1.6	0.9–2.0	0.054
Patient Characteristics					
Male, n (%)	26	51%	38	62%	0.228
Age[a], years	61	26–83	62	29–83	0.58
Race other than East Asian, n (%)	0	0%	1	2%	N/A
Weight, kg	64	41–94	61	37–91	0.341
BMI[a], kg/m^2	24	20–26	20	18–21	**<0.001**
Obesity (BMI>30kg/m^2), n (%)	6	12%	1	2%	**0.046**
Target trough 15–20 μg/Mℓ, n (%)	14	27%	26	43%	0.095
Baseline eGFR, mL/min/1.73 m^2	94	74–108	96	80–109	0.343
Renal replacement therapy, n (%)	2	4%	6	10%	0.287
Final eGFR, mL/min/1.73 m^2	2	4%	6	10%	0.287
Co-morbidities					
Malignancy, n (%)	24	47%	27	44%	0.767
Cardiovascular, n (%)	3	6%	10	16%	0.137
Pulmonary, n (%)	1	2%	0	0%	N/A
Central nervous system, n (%)	1	2%	3	5%	0.624
Gastrointestinal, n (%)	5	10%	5	8%	1
Diabetes, n (%)	11	22%	9	15%	0.348
Site of Infection					
Respiratory, n (%)	1	2%	7	11%	0.069
Bloodstream, n (%)	6	12%	4	7%	0.508
Skin and soft tissue, n (%)	11	22%	18	30%	0.339
Central nervous system, n (%)	2	4%	6	10%	0.287
Bone/Joint, n (%)	5	10%	7	11%	1
Intra-abdominal, n (%)	9	18%	10	16%	0.86
Ear, nose, and throat, n (%)	15	29%	6	10%	**0.008**
Urinary tract, n (%)	2	4%	3	5%	1
Positive culture result[c]	25	49%	28	46%	0.742
MRSA, n (%)	7	14%	14	23%	0.213
MRCNS, n (%)	3	6%	2	3%	0.658
MSSA, n (%)	11	22%	13	21%	0.974
Enterococcus sp., n (%)	3	6%	7	11%	0.342
Other gram positives[d], n(%)	9	18%	10	16%	0.86
Concurrent nephrotoxic agents[e]	25	49%	35	57%	0.377
Piperacillin/tazobactam, n (%)	14	27%	24	39%	0.186
Furosemide, n (%)	10	20%	13	21%	0.824
ACE inhibitor or ARBs, n (%)	3	6%	1	2%	0.329
Aminoglycosides, n (%)	0	0%	2	3%	N/A
Vasopressin, n (%)	0	0%	0	0%	N/A

(*Continued*)

Table 6 (Continued).

	Non-PKCS (n=51)	% or IQR	PKCS (n=61)	% or IQR	*P* value
Initial CRP[f], mg/dL	1.7	0.4–5.0 (n=40)	3.6	1.4–7.3 (n=60)	**0.031**
Initial WBC count[f],/mL	6.7	4.7–9.0 (n=43)	7.2	5.1–10.4 (n=60)	0.286

Notes: [a]All of the values were described in median with interquartile range (IQR) given their non-normal distribution except for daily dose, age, and BMI which followed normal distribution, and was described in mean with range and compared with independent sample *t*-test. [b]Time to target attainment was compared between PKCS group patients who received their first PKCS within 72h from the start of vancomycin therapy and achieved target trough (n=36) and non-PKCS group patients who achieved target trough (n=37). [c]Infection with two microorganisms indicated for vancomycin existed (4 cases in PKCS group). [d]Other gram positives include *Streptococcus* species, *Corynebacterium* species, *Propionibacterium acnes*, and *Bacillus cereus*. [e]Patients using two or more concurrent nephrotoxic agents existed (5 cases in PKCS group, 4 cases in non-PKCS group). [f]Patients without the result of CRP and WBC count existed. Significant values are indicated in bold.

Abbreviations: PKCS, pharmacokinetic consultation service; IQR, interquartile range; VIN, vancomycin induced nephrotoxicity; N/A, not applicable; BMI, body mass index; eGFR, estimated glomerular filtration rate; MRSA, methicillin resistant *Staphylococcus aureus*; MRCNS, methicillin resistant coagulase negative *Staphylococcus*; MSSA, methicillin susceptible *Staphylococcus aureus*; ACE inhibitor, Angiotensin-converting enzyme inhibitor; ARBs, Angiotensin II receptor blockers; CRP, C-reactive protein; WBC, white blood cell.

revealed improved clinical outcome including lower 30-day mortality rate.[20,32,37] Only one out of six studies that evaluated clinical outcome implemented retrospective study design, however, due to small sample size (n=43), all of the study results failed to demonstrate statistical significance.[43] Among the studies that evaluated trough-based PK-guided dosing, three targeted MRSA patients,[35,37,38] two targeted ICU patients,[25,65] and one targeted CKD patients.[43] In another two studies conducted in adult patients, the patient inclusion criteria were relatively broad.[20,32] Our study population only included patients from the general ward of the surgery department to minimize heterogeneity in the patient population. To the best of our knowledge, our study has strengths in that we investigated the status of vancomycin TDM and PK-guided dose adjustment in a clinical setting with a large sample size (2412 patients), and that we evaluated the effects of PK-guided dosing with a large and homogeneous patient population.

In a retrospective cohort study conducted by Dorajoo et al,[43] the clinical effect of trough-based PK dosing guided by the web-based tool, VancApp was evaluated with a total of 43 CKD patients (creatinine clearance (CrCl) < 60 mL/min, based on the Cockcroft–Gault equation using total body weight).

Table 7 Logistic Regression Analysis for Treatment Failure Rate and Development of VIN in Patients with Positive Culture Result

	Treatment Failure				VIN			
	Univariate		Multiple		Univariate		Multiple	
Covariate	**OR**	***P* value**	**OR (95% CI)**	***P* value**	**OR**	***P* value**	**OR**	***P* value**
Group (PKCS)	1.22	0.743			2.19	0.362		
Duration of vancomycin therapy	1.01	0.675			0.95	0.405		
Daily dose of vancomycin	1.02	0.562			1.01	0.805		
Target trough attainment	1.67	0.433						
Time to initial target trough	**0.67**	**0.003**	**0.64 (0.50–0.85)**	**0.002**				
BMI	1.12	0.225			0.94	0.582		
Baseline eGFR	0.99	0.516			1.01	0.528		
Renal replacement therapy	0.83	0.866			N/A	1		
Malignancy	1.78	0.374			0.46	0.362		
Diabetes	**0.38**	**0.15**	0.26 (0.04–1.98)	0.195	1.93	0.452		
Skin and soft tissue infection	**0.30**	**0.053**	0.48 (0.07-3.37)	0.46	2.28	0.301		
MRSA	0.61	0.422			0.83	0.807		
MRSA MIC ≤0.5 mg/L	1.17	0.826			1.05	0.957		
Initial CRP	0.96	0.385			1.03	0.702		
Concurrent nephrotoxic agent use	0.20	**0.044**	N/A	1	**5.67**	**0.114**	N/A	1

Note: Significant values are indicated in bold.

Abbreviations: VIN, vancomycin induced nephrotoxicity; OR, odds ratio; CI, confidence interval; PKCS, pharmacokinetic consultation service; BMI, body mass index; eGFR, estimated glomerular filtration rate; MRSA, methicillin resistant *Staphylococcus aureus*; MIC, minimum inhibitory concentration; CRP, C-reactive protein; N/A, not applicable.

Table 8 Clinical Outcome Analysis of Patients with MRSA Infection

	Non-PKCS (n=25)	% or IQR	PKCS (n=28)	% or IQR	*P* value
Treatment failure rate, n (%)	5	20%	2	7%	0.234
Duration of vancomycin therapy, days	7	5–12	13	8–17	**0.003**
Daily dose of vancomycin[a], mg/kg/day	36	9–67	29	4–50	0.071
Incidence of VIN, n (%)	2	8%	1	4%	0.597
Target trough attainment rate, n (%)	18	72%	20	71%	0.963
Time to initial target trough[b], days	3.9	3.0–4.6	2.3	1.8–3.4	**0.02**
No. of trough measurement per day, n	3.9	2.7–4.7	3.9	3.1–4.9	0.748
No. of dose adjustment per week, n	1.4	0.0–1.9	1.6	0.8–2.1	0.219
Patient Characteristics					
Initial CRP[c]. mg/dL	1.1	0.3–3.5	3.3	1.3–6.8	0.076
Initial WBC count[c],/mL	6.9	4.9–9.0	8	5.4–12.1	0.138
Site of infection					
Respiratory, n (%)	0	0%	3	11%	N/A
Blood stream, n (%)	4	16%	0	0%	N/A
Skin and Soft Tissue, n (%)	4	16%	10	36%	0.104
Central Nervous System, n (%)	0	0%	3	11%	N/A
Bone/Joint, n (%)	0	0%	3	11%	N/A
Intra-abdominal, n (%)	2	8%	3	11%	0.736
Ear, nose and throat, n (%)	15	60%	6	21%	**0.004**
MRSA MIC					
≤0.5 mg/L, n (%)	17	68%	12	43%	0.114
1 mg/L, n (%)	6	24%	16	57%	**0.015**
2 mg/L, n (%)	2	8%	0	0%	N/A

Notes: [a]All of the values were described in median with interquartile range (IQR) given their non-normal distribution except for daily dose which followed normal distribution, and was described in mean with range and compared with independent sample *t*-test. [b]Time to target attainment was compared between PKCS group patients who received their first PKCS within 72 h from the start of vancomycin therapy and achieved target trough (n=15) and non-PKCS group patients who achieved target trough (n=18). [c]Patients without the result of CRP and WBC count existed. Significant values are indicated in bold.

Abbreviations: MRSA, methicillin resistant *Staphylococcus aureus*; PKCS, pharmacokinetic consultation service; IQR, interquartile range; VIN, vancomycin induced nephrotoxicity; MIC, minimum inhibitory concentration; CRP, C-reactive protein; WBC, white blood cell; N/A, not applicable.

The time it took to reach target trough, length of hospitalization, 30-day mortality rate, 30-day readmission rate, and development of nephrotoxicity was compared between 22 patients whose vancomycin dosing was guided by VancApp and 21 patients who received the usual vancomycin dosing of weight-based doses of 15–20 mg/kg administered at interval of 12 or 24h. Patients who received the VancApp-guided dosing took a shorter time to reach the target trough (median: 66 vs 102 h, $P = 0.187$), had longer hospitalization, fewer 30-day mortalities, fewer 30-day readmission, and higher rate of nephrotoxicity compared to the patient who received usual vancomycin dosing. However, statistical significance was not attained due to the small study population. In respect to the time it took to reach the target trough, the results differed from our results, as our study showed no significant difference between the intervention and control group (PKCS (n=126) vs non-PKCS (n=132), median 4.2 (101) vs 3.6 (86) days (h), $P = 0.430$). This gap between the results could have originated from the difference in the study population. Contrary to the study by Dorajoo et al which only involved CKD patients and excluded patients who received renal replacement therapy, we involved patients regardless of renal function and the application of renal replacement therapy. In our study, only 10% of patients (16 out of the PKCS group, 11 out of the non-PKCS group) had estimated GFR less than 60 mL/min/1.73m^2 (calculated using CKD-EPI equation).

Hirano et al conducted a pre-post intervention study to assess the effect of pharmacist-managed dose adjustment in adult patients with definite MRSA infection.[35] Although the percentage of patients with serum vancomycin

Table 9 Comparison of Duration of Vancomycin Therapy Between Groups with or without the Possible Cause of Longer Duration of Therapy

	Duration of Vancomycin Therapy, Days, Median (IQR)	*P* value
Non-PKCS vs PKCS group	**6.0 (4.0–8.25) vs 9.0 (5.0–15.0)**	**<0.001**
Concurrent nephrotoxic agent use (no vs yes)	7.5 (5.0–13.8) vs 7.0 (4.3–11.0)	0.144
Target range (10–15 vs 15–20 mg/L)	7.0 (5.0–11.0) vs 7.0 (4.0–13.0)	0.958
Obesity (BMI ≤30 vs >30 kg/m2)	7.0 (5.0–12.0) vs 9.0 (4.5 vs 11.5)	0.713
Sex (Female vs Male)	7.0 (5.0–12.0) vs 7.0 (4.0–11.0)	0.671
Malignancy (No vs Yes)	7.0 (5.0–12.0) vs 7.0 (4.0–11.0)	0.302
DM (No vs Yes)	7.0 (4.0–11.0) vs 7.0 (5.0–13.0)	0.516
Site of infection (No vs Yes)		
Skin and soft tissue	7.0 (4.0–12.0) vs 8.0 (5.0–12.3)	0.214
Bone and joint	**7.0 (4.0–11.0) vs 8.5 (5.0–14.0)**	**0.006**
Blood stream	**7.0 (5.0–13.0) vs 4.5 (3.0–7.0)**	**<0.001**
Respiratory	7.0 (5.0–11.8) vs 8.0 (4.3 vs 14.5)	0.691
Central Nervous System	7.0 (4.0–12.0) vs 7.5 (5.3 vs 22.3)	0.264
Empirical use (No vs Yes)	8.0 (5.0–13.5) vs 7.0 (4.0–11.0)	0.066
MRSA infection (No vs Yes)	7.0 (4.0–11.0) vs 8.5 (5.0–14.0)	0.053

Note: Significant values are indicated in bold.
Abbreviations: PKCS, pharmacokinetic consultation service; IQR, interquartile range; BMI, body mass index; MRSA, methicillin-resistant *Staphylococcus aureus*.

concentrations within the therapeutic range (10–20 μg/mL) and the percentage of patients who attained target PK/PD parameters (AUC_{24}/MIC >400) was significantly higher in the post-implementation group, no significant difference was observed in length of hospitalization and 30-day mortality rate after the initiation of vancomycin.

Another pre-post intervention study compared the vancomycin treatment failure rate in patients with MRSA bacteremia between pre (n=49) and post-implementation (n=28) of pharmacy-led vancomycin dosing.[37] A time prolongation to treatment failure was noted in the intervention group ($P = 0.011$, log rank test) and pharmacist intervention was the only parameter that demonstrated a significant hazard ratio for vancomycin treatment failure (hazard ratio 0.26, $P = 0.014$). This means that the intervention group took a longer time until vancomycin treatment failure, and the intervention was the only factor causing significant effect on the time until vancomycin treatment failure. This result is discordant with our result, which demonstrated no difference in treatment failure rate and PKCS showed no significant results for treatment failure in logistic regression analysis. We could assume that this discordance in outcome could have originated from the difference in study design (pre-post intervention study vs retrospective observational study) or in the study population (patients with MRSA bacteremia vs patients with any MRSA infection).

Our study possesses important limitations worth discussing. First, our study used trough concentration as the surrogate marker. The revised consensus guidelines for TDM of vancomycin recommend AUC-guided dosing and monitoring for patients with suspected or definitive serious MRSA infections.[9] However, implementation of AUC monitoring is challenging in routine clinical practice (ie, investment in Bayesian software, training and education of pharmacists, physicians, phlebotomists, and nursing staff on the revised guidelines),[55,56,58] that a multicenter cross-sectional electronic survey showed that less than a quarter (18/78, 23.1%) of respondent medical centers were providing AUC-based monitoring.[56] Compared to AUC, monitoring trough concentration is easily applicable in medical centers with a readily available serum vancomycin concentration assay.[58] Moreover, although the evidence for the recommendations has been strengthened compared to the previous guideline and a number of studies have shown better efficacy and safety outcomes through AUC monitoring since the publication of the revised guideline[18,22,24,28,48,52–54,62–64], there are no randomized controlled trials. Given the challenging prerequisites for implementing AUC monitoring and the absence of high-quality evidence, it is still difficult to endorse conversion from trough to AUC monitoring.

Furthermore, although several studies have demonstrated an improved outcome of the AUC monitoring in infections other than severe MRSA infections the revised guidelines cover solely severe MRSA infections and advise caution

against extrapolation to infections other than severe MRSA infections.[9]

Our study used trough concentration as the surrogate marker. However, considering the impracticality of AUC monitoring, the relatively short period of time since its introduction, and the scope of the recommendation covering solely severe MRSA infections, the importance of our study should not be underestimated.

Secondly, for the evaluation of clinical outcome, we were limited by a small sample size owing to the strict patient selection criteria to avoid bias. For this reason, some necessary statistical analyses could not be performed and the possibility for type 2 error could not be excluded. However, to the best of our knowledge, this study included the largest number of patient for a clinical outcome assessment in any retrospective observational study conducted to date. Thirdly, although we tried our best to select patients with similar clinical characteristics, population heterogeneity exists. Nevertheless, no significant difference was observed in baseline characteristics between the PKCS and non-PKCS group and we performed logistic regression analysis to ensure that any difference in baseline characteristics did not affect the outcome assessment.

Conclusion

PK-guided dosing has been proved effective in a specific patient population, including those critically ill, with chronic kidney disease or with MRSA bacteremia. However, in our study with non-critical patients, although PKCS increased the achievement of target trough concentration, it did not lead to a higher treatment success rate, shorter duration of vancomycin treatment, or decreased VIN in vancomycin treatment. With this result, we wish to add to the growing body of literature regarding the clinical effectiveness of pharmacokinetic dose adjustment.

Abbreviations

PK, pharmacokinetic; PKCS, pharmacokinetic consultation service; TDM, therapeutic drug monitoring; VIN, vancomycin-induced nephrotoxicity; MRSA, methicillin-resistant *Staphylococcus aureus*; MIC, minimum inhibitory concentration; AUC_{24}/MIC_{BMD}, ratio of area under the curve over 24 hours to MIC determined by broth microdilution; PK/PD, pharmacokinetic/pharmacodynamics; GFR, glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; KIMS, kinetic interaction of microparticles in solution; IQR, interquartile range; BMI, body mass index; MRCNS, methicillin-resistant coagulase negative *Staphylococcus*; ACE inhibitor, Angiotensin-converting enzyme inhibitor; ARBs, Angiotensin II receptor blockers; OR, odds ratio; CrCl, creatinine clearance.

Ethical Approval

This study was performed with the approval of the Institutional Review Board of Samsung Medical Center (approval number: SMC 2017-12-038-004). Furthermore, this study was conducted in accordance with the Declaration of Helsinki.

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

The authors declare no conflicts of interest.

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