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MAJOR ARTICLE

Implementation of a Pharmacist-Driven Vancomycin Area Under the Concentration-Time Curve Monitoring Program Using Bayesian Modeling in Outpatient Parenteral Antimicrobial Therapy

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Background. Current vancomycin monitoring guidelines recommend monitoring 24-hour area under the concentration-time curve (AUC) to minimum inhibitory concentration ratios for patients with serious methicillin-resistant *Staphylococcus aureus* infections. However, there are sparse data on the safety, feasibility, and efficacy of vancomycin AUC monitoring for outpatients. Traditional AUC pharmacokinetic calculations require 2 concentrations, while bayesian software allows for single-concentration AUC estimations.

Methods. We conducted a single-center, quasi-experimental, interrupted time series study of patients enrolled in the outpatient parenteral antimicrobial therapy program at our institution for vancomycin management. Our institution implemented a pharmacist-driven vancomycin AUC monitoring program from September 2019 to February 2020, and again from September 2022 to March 2023. Patients enrolled underwent vancomycin monitoring using an AUC goal of 400–600 mg·h/L, estimated through bayesian modeling. Patients enrolled in the outpatient parenteral antimicrobial therapy program from July 2021 through August 2022 for trough-based monitoring were used for comparison. The primary outcome was nephrotoxicity incidence, defined as a serum creatinine increase by ≥0.5 mg/dL or ≥50% during outpatient vancomycin therapy.

Results. We enrolled 63 patients in the AUC group and 60 patients in the trough-based group. Nephrotoxicity was significantly lower in the AUC cohort (6.3% vs 23.3%; $P = .01$). The number of unusable vancomycin concentrations was also significantly lower in the AUC cohort (0% vs 6%; $P < .01$). There was no difference in composite 90-day all-cause mortality or readmission (33.3% vs 38.3%; $P = .56$).

Conclusions. Following implementation of a pharmacist-driven AUC monitoring program, patients were less likely to develop nephrotoxicity during outpatient vancomycin therapy.

Keywords. vancomycin; OPAT; Therapeutic-drug-monitoring; bayesian modeling.

Vancomycin is a mainstay of therapy for infections caused by methicillin-resistant *Staphylococcus aureus* and a variety of other gram-positive organisms. Despite its widespread use, there are major nephrotoxicity concerns for patients receiving vancomycin. Historical estimates of vancomycin-induced nephrotoxicity range from 5% to 43% [1]. Due to toxicity concerns, vancomycin dosing has evolved from every-12-hour fixed administration to patient-specific regimens. Therapeutic drug monitoring balances efficacy and safety concerns and remains a routine part of vancomycin therapy.

Both in vitro and in vivo studies have demonstrated that an area under the concentration-time curve (AUC) to minimum inhibitory concentration ratio ≥400 is the pharmacokinetic-pharmacodynamic property most associated with vancomycin bacterial killing [2, 3]. However, vancomycin therapeutic drug monitoring has traditionally consisted of trough-based monitoring to a goal of 15–20 mg/L as a surrogate for AUC estimations [4]. Trough monitoring was recommended over AUC monitoring due to operational feasibility and positive correlation between troughs ≥15 mg/mL and AUC ≥400 mg·h/L. Since the first vancomycin monitoring guidelines were released

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in 2009, newer studies have demonstrated that trough concentrations ≥15 mg/mL are correlated with an increased risk of nephrotoxicity [1]. Given that trough concentrations <15 mg/L have unreliable probability of AUC ≥400 mg·h/L, studies shifted to focus on the practicality of AUC monitoring.

In vivo studies have shown a positive correlation between AUC and renal dysfunction. A statistically significant increase in nephrotoxicity rates has been seen with AUC values ≥563 [5]. A 2022 meta-analysis comparing AUC-guided dosing with trough-based monitoring found significantly lower rates of vancomycin-induced acute kidney injury in the AUC group, with an odds ratio of 0.63 (95% confidence interval, .47–.83; $P = .001$) [6]. Because of this, vancomycin monitoring guidelines were updated in 2019, with recommendations to use AUC goals of 400–600 mg·h/mL for the majority of inpatients on vancomycin [7].

While vancomycin AUC monitoring is being increasingly used for inpatients, limited studies have investigated feasibility for outpatients. Barriers to outpatient implementation include difficulty obtaining 2 timed vancomycin concentrations for pharmacokinetic calculations, limited pharmacist involvement, and lack of laboratory timing accuracy. To overcome these barriers, medical centers have used AUC-based trough goals during outpatient parenteral antimicrobial therapy (OPAT) as a surrogate marker with favorable outcomes [8]. Others have used continuous-infusion vancomycin, which eliminates the need for true trough timing with the added benefit of a potential reduction in renal dysfunction [9–12].

Vancomycin monitoring guidelines recommend using bayesian modeling software when available for pharmacokinetic calculations [7]. Bayesian modeling uses population-based pharmacokinetic principles to augment patient-specific values. These models have demonstrated high accuracy using both 2- and 1-concentration sampling, compared with traditional first-order pharmacokinetic calculations [13, 14]. Bayesian modeling can perform calculations with any vancomycin concentration time, allowing for additional flexibility outside of traditional peak and trough concentrations. To our knowledge, no studies to date have investigated clinical outcomes using bayesian modeling estimations for outpatient vancomycin therapy. The purpose of this study is to evaluate the safety and efficacy of a pharmacist-driven vancomycin AUC monitoring program using bayesian modeling in an OPAT program.

METHODS

Study Design

This was a single-center, quasi-experimental, interrupted time series study comparing trough-based vancomycin monitoring with pharmacist-driven AUC monitoring for patients enrolled in the OPAT program at Brigham and Women's Hospital (BWH), a tertiary academic medical center. Study time periods included September 2019 through February 2020 (AUC 1) and September 2022 through March 2023 (AUC 2) for pharmacist-driven AUC monitoring, while the trough-based monitoring cohort was collected from July 2021 through August 2022. This study was approved by the Mass General Brigham institutional review board.

Patient Consent Statement

This study was approved through the institutional review board as a minimal harm protocol. The study does not include factors necessitating patient consent.

Eligibility Criteria

All patients enrolled in the OPAT program for vancomycin monitoring during the above time frames were screened for inclusion. The BWH OPAT REDCap database was used to identify patients for inclusion. Patients referred to the OPAT program are manually entered into the REDCap database at the time of referral. Patients were excluded if they were receiving renal replacement therapy at the time of OPAT enrollment, enrolled in the OPAT program for <72 hours and had <2 vancomycin concentrations assessed, or had no laboratory samples for >14 days during OPAT vancomycin therapy or if their infectious diseases (ID) clinician opted out of AUC-based monitoring.

OPAT Workflow

The OPAT program at BWH comprised an ID clinician, a nurse practitioner, 3 registered nurses, and an administrative assistant. OPAT antimicrobials are supplied by an external infusion pharmacy. Laboratory sample collections were performed by a visiting nurse association (VNA) or at a regional clinical laboratory. Results are then either faxed to the OPAT team or transmitted electronically to the patient's electronic medical record (EMR). The OPAT program works in tandem with the patient's outpatient ID clinician. Laboratory monitoring and management of intervisit issues, such as changes in symptoms or issues with intravenous access, are performed by the OPAT team, and any abnormal results, clinical issues, or proposed changes are communicated to the outpatient ID clinician for review and approval.

Within 48 hours of hospital discharge, an OPAT registered nurse confirms the OPAT antimicrobial regimen with the infusion pharmacy and laboratory schedule with the VNA, if applicable. For patients receiving vancomycin, the standard practice is to assess a vancomycin serum trough concentration within 48 hours of hospital discharge and then with weekly safety laboratory panels thereafter. The standard safety laboratory panel includes serum creatinine, serum urea nitrogen, liver function tests, complete blood cell count with differential, and a vancomycin serum trough concentration. Additional laboratory testing can be requested ad hoc by the outpatient ID clinician.

A pharmacist-driven, vancomycin AUC monitoring program was implemented from September 2019 to February 2020 and again starting in September 2022. During pharmacist-driven time periods, patients underwent vancomycin AUC monitoring with a goal of 400–600 mg·h/L. Single-concentration AUC calculations were performed using a web-based bayesian modeling program based on established vancomycin pharmacokinetic models [15–17]. Before hospital discharge, the pharmacist optimized the vancomycin dosing using AUC goals. After discharge, dosing times were confirmed to ensure accurate AUC estimations. Following vancomycin concentrations and safety laboratory panels, the pharmacist calculates new patient-specific AUC values. Dosing recommendations were communicated to the outpatient ID clinician and OPAT personnel as applicable. During the time period when a pharmacist was not working with the OPAT program, vancomycin trough targets were set by the referring or outpatient ID clinician, generally ranging between 10 and 20 mg/L.

Outcomes and Data Collection

The primary safety outcome was nephrotoxicity, defined as a serum creatinine increase of ≥0.5 mg/dL or ≥50% during outpatient vancomycin therapy to maintain consistency with prior studies [7]. The secondary efficacy outcome was a 90-day composite of all-cause mortality and all-cause hospital readmission. Additional secondary outcomes included the individual components of the composite, early vancomycin discontinuation due to adverse events (AEs), and the number of unusable vancomycin concentrations during outpatient therapy. An unusable vancomycin concentration was defined as a vancomycin concentration time that could not be verified and/or a mistimed concentration that could not be used for clinical decision making, as noted in the patients EMR.

Patient demographics, pertinent comorbid conditions, concomitant nephrotoxic medications, vancomycin indications, vancomycin concentrations, vancomycin regimens including dose changes, and new-onset nonnephrotoxic vancomycin-related AEs as noted in the EMR were also collected. The pertinent comorbid conditions recorded were chronic kidney disease, diabetes mellitus, heart failure, and obesity. Nephrotoxic medications collected were angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors, aminoglycosides, loop diuretics, piperacillin-tazobactam, and calcineurin inhibitors/mammalian target of rapamycin inhibitors. New-onset nonnephrotoxic vancomycin related AEs screened for included eosinophilia (>500 cells/μL), neutropenia (<500 cells/μL), and rash (documented in the EMR). All data were collected from the patients' EMRs and recorded in the OPAT REDCap database.

Statistical Analysis

Analyses were performed to compare outcomes between the pharmacist-driven AUC monitoring cohort and the non–pharmacist-driven trough-based monitoring cohort. The primary outcome and categorial secondary outcomes were compared using χ^2 or Fisher exact tests as appropriate. To identify potential variables associated with nephrotoxicity, a multivariable regression analysis was performed. Factors selected a priori were pharmacist-driven AUC monitoring, age (continuous), obesity (body mass index ≥30 [calculated as weight in kilograms divided by height in meters squared] during outpatient vancomycin therapy), use of ≥1 concomitant nephrotoxic medication, and duration of OPAT therapy (continuous). Differences were considered statistically significant at $P \leq .05$. All statistical analyses were performed using Stata software (version 17.0; StataCorp).

RESULTS

Demographics

A total of 152 patients were screened for inclusion, with 123 included in the final analysis (Figure 1). In total, 63 patients underwent pharmacist-driven vancomycin monitoring using AUC goals, and 60 underwent trough-based monitoring without dedicated pharmacist involvement.

Overall, baseline demographics were similar between groups (Table 1). There were numerically more patients receiving vancomycin for bone and joint infections, as well as more *S aureus* infections, in the pharmacist-driven AUC cohort. In the trough-based cohort, there were higher rates of obesity. The median age was 64 years, and similar initial weight-based vancomycin doses were used in both groups. Most patients in both cohorts did not have pertinent comorbid conditions or

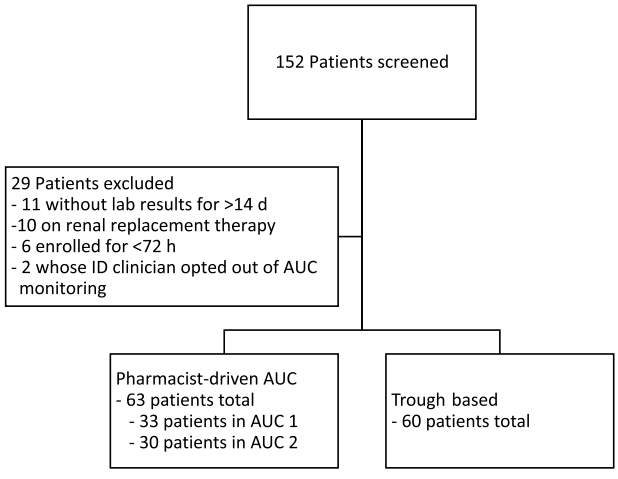

Figure 1. Patient enrollment. Abbreviations: AUC, area under the concentration-time curve; ID, infectious diseases.

Table 1. Baseline Patient Characteristics

Characteristic	Patients, No. (%)[a]	
	Pharmacist-Driven AUC Cohort (n = 63)	Trough Cohort (n = 60)
Female sex	32 (50.8)	26 (43.3)
Age, median (IQR), y	64 (56–76)	64 (51–71)
Weight, median (IQR), kg	74.4 (59.0–83.9)	79.6 (69.6–100.4)
Height, median (IQR), cm	167.6 (162.0–177.8)	170.2 (162.6–179.7)
Comorbid conditions		
CKD	6 (9.5)	11 (18.3)
DM	16 (25.4)	20 (33.3)
HF	8 (12.7)	6 (10.0)
Obesity	9 (14.3)	21 (35.0)
Concomitant medications		
ACEi/ARB/ARNI	17 (27.0)	14 (23.3)
Aminoglycoside	0	1 (1.7)
Loop diuretic	13 (20.6)	11 (18.3)
Piperacillin-tazobactam	0	1 (1.7)
Vancomycin indication		
Bacteremia	17 (27.0)	16 (26.6)
Bone/joint	36 (57.1)	23 (38.3)
CNS	1 (1.6)	1 (1.7)
Endocarditis	6 (9.5)	8 (13.3)
Pulmonary	3 (4.8)	4 (6.6)
SSTI	4 (6.3)	6 (10.0)
UTI	1 (1.6)	4 (6.6)
Other	11 (17.5)	9 (15.0)
Organism		
Staphylococcus aureus	27 (43)	21 (35)
CoNS	26 (41)	22 (37)
Streptococcus sp.	5 (8)	7 (12)
Enterococcus sp.	6 (10)	8 (13)
No organism identified	7 (11)	7 (12)
Other[b]	7 (11)	11 (18)
Initial vancomycin dose, median (IQR), mg/kg	28.0 (18.5–34.9)	26.2 (18.3–34.9)
Total duration of outpatient vancomycin therapy, d	1816	1498
Total concentrations obtained, no.	205	267

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease; CNS, central nervous system; CoNS, coagulase negative staphylococcus; DM, diabetes mellitus; HF, heart failure; IQR, interquartile range; SSTI, skin and soft-tissue infection; UTI, urinary tract infection.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]"Other" included diabetic foot infection, ear, nose, and throat infection, epidural abscess, graft infection, and intra-abdominal infection.

concomitant nephrotoxic medications. In total, there were 1816 days of outpatient vancomycin therapy in the pharmacist-driven AUC cohort and 1498 days in the trough-based cohort. A total of 205 concentrations were obtained in the pharmacist-driven AUC cohort (0.11/vancomycin-day), compared with 267 concentrations in the trough-based cohort (0.18/vancomycin-day).

Table 2. Outcomes by Cohort

Outcome	Patients, No. (%)		
	Pharmacist-Driven AUC Cohort (n = 63)	Trough Cohort (n = 60)	*P* Value
Nephrotoxicity	4 (6.3)	14 (23.3)	.01
90-d Composite	21 (33.3)	23 (38.3)	.56
All-cause mortality	2 (3.2)	3 (5)	.68
All-cause readmission	20 (31.7)	23 (38.3)	.44
Reason for readmission			
Index infection	5 (7.9)	9 (15.0)	.26
Vancomycin-related AE	1 (1.6)	2 (3.3)	.61
Other[a]	14 (22.2)	12 (20.0)	.76
Early vancomycin discontinuation due to AE	3 (4.8)	11 (18.3)	.02
Unusable concentrations, no. (%)[b]	0 (0)	16 (6.0)	<.001

Abbreviations: AUC, area under the concentration-time curve; AE, adverse event.

[a]"Other" included nonindex infectious process (n = 8), cardiac event (n = 5), cancer (n = 3), planned surgery (n = 3), and altered mental status, gout, groin wound, hypokalemia, non–vancomycin-related medication AE, transfusion-related lung injury, and unclear (each n = 1).

[b]Percentages based on 205 concentrations in the pharmacist-driven AUC cohort and 267 in the trough-based cohort.

Table 3. Multivariable Regression Analysis

Variable	OR (95% CI)	*P* Value
Pharmacist-driven AUC monitoring	0.18 (.05–.63)	.007
Age	1.01 (.97–1.05)	.68
Obesity	0.51 (.13–1.98)	.33
Concomitant number of nephrotoxic medications	1.34 (.62–2.92)	.46
OPAT duration	1.01 (.98–1.05)	.50

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; OPAT, outpatient parenteral antimicrobial therapy; OR, odds ratio.

Outcomes

The primary safety outcome of nephrotoxicity occurred in 4 patients (6.3%) in the pharmacist-driven AUC cohort, compared with 14 (23.3%) in the trough-based cohort ($P = .01$) (Table 2). This result was consistent in a subgroup analysis of patients without baseline chronic kidney disease (7.0% vs 20.4%; $P = .049$). Only pharmacist-driven AUC monitoring was associated with a significant difference in nephrotoxicity rates in the multivariable regression analysis, which remained statistically significant when controlling for all other independent variables (adjusted odds ratio, 0.17 [95% confidence interval, .05–.61]; $P = .006$) (Table 3). There was no difference in 90-day all-cause mortality or hospital readmission between the pharmacist-driven AUC and trough cohorts (hospital readmissions, 20 [31.7%] and 23 [38.3%], respectively). Outcomes were similar between pharmacist-driven AUC cohorts (Figure 2). There was also no difference between groups in index infection–related readmission, vancomycin AE–related readmission, or other reasons for readmission (Table 2).

Significantly less vancomycin discontinuation due to AEs occurred in the pharmacist-driven AUC cohort than in the

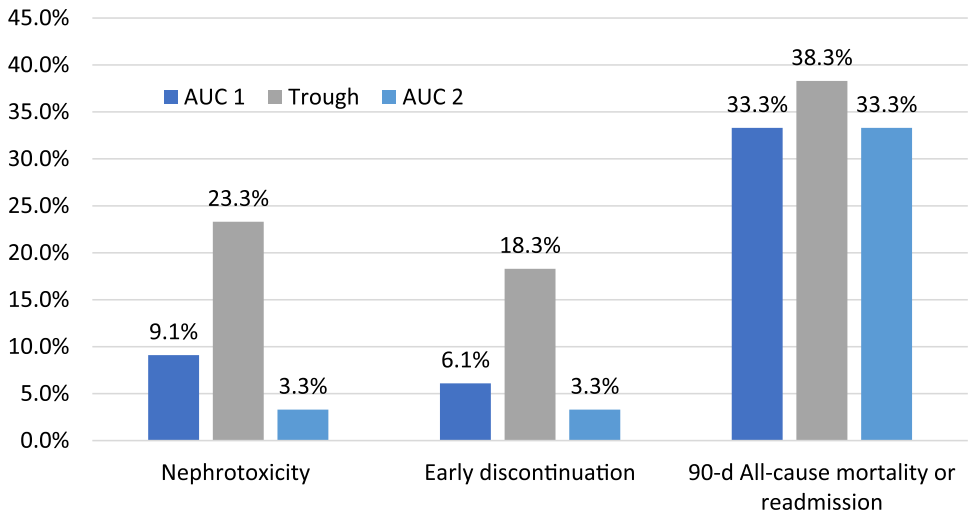

Figure 2. Vancomycin efficacy and safety outcomes. Abbreviation: AUC, area under the concentration-time curve.

trough cohort (4.8% vs 18.3%, respectively; $P = .02$) (Table 2). There were also significantly fewer unusable concentrations in the pharmacist-driven AUC cohort (0 vs 16 concentrations; $P = .002$). There was no significant difference in the number of dose changes between the 2 cohorts (47 dose vs 61 dose changes; $P = .73$).

DISCUSSION

This single-center quasi-experimental interrupted time series study evaluating a pharmacist-driven vancomycin AUC monitoring program during OPAT therapy found a significant reduction in the primary safety outcome of nephrotoxicity, compared with trough-based monitoring. There were also significant reductions in vancomycin discontinuation due to AEs and fewer unusable concentrations in the pharmacist-driven AUC cohort. There was no difference in the secondary 90-day composite efficacy outcome of all-cause mortality or all-cause hospitalization.

With multiple studies demonstrating improved clinical and financial outcomes using OPAT compared with continued inpatient antimicrobial administration, there is an interest in expanding OPAT programs [18–20]. Given the high rates of complications using vancomycin, improvement in outpatient vancomycin monitoring is needed [21, 22]. Nephrotoxicity is among the most commonly identified vancomycin-related AEs and—unlike with others, such as rash—dosing can be optimized to mitigate the risk of acute kidney injury during therapy. Conversion from trough-based monitoring to AUC monitoring has been shown to significantly reduce renal dysfunction for the inpatient population and has been widely adopted in many hospitals [6]. However, there are limited data describing the role of AUC monitoring during outpatient vancomycin therapy.

Complex pharmacokinetic calculations, limited personnel experience, and difficulty coordinating accurately timed serum concentrations may contribute to the minimal adoption of AUC-based monitoring for vancomycin in OPAT programs. As demonstrated in this study, ID pharmacists are uniquely suited to overcome these challenges and improve vancomycin therapy [23]. ID pharmacists can navigate pharmacokinetic calculations, coordinate with the patient and other members of the healthcare team, and monitor laboratory findings during an OPAT course. While traditional 2-concentration AUC calculations may not be feasible for outpatients due to limited VNA availability, bayesian modeling allows for single concentration AUC calculations without compromising accuracy [14].

To our knowledge, this is the first study investigating clinical outcomes with bayesian AUC modeling during outpatient vancomycin therapy, and the second using a pharmacist-driven AUC-based monitoring program for intermittent vancomycin infusions in the outpatient setting [8]. Our findings are similar to those in the study by Rees et al [8], demonstrating a decrease in nephrotoxicity after implementation of AUC monitoring. While Rees et al used AUC-derived trough goals, our protocol used a bayesian modeling software. Bayesian software allows for more flexible concentration timing. Instead of needing true trough values, a concentration obtained at any time can be added to the model for individual pharmacokinetic assessment. This significantly decreased the number of unusable concentrations in our pharmacist-driven AUC cohort, which previously occurred at a rate of 6%. Coordinating repeated sampling is a time-intensive process for the OPAT team and may be limited by VNA availability. This can lead to delays in dose optimization, which may increase the risk of AEs or treatment failure.

Data suggest that pharmacist assessment of bayesian modeling does not require significant time resources [24]. Other programs have successfully implemented continuous infusion vancomycin during OPAT [9–12]. Continuous infusion offers benefits similar to those of bayesian modeling, as any concentration can be used to extrapolate AUC. However, continuous infusions may be burdensome for patients due to the 24-hours-per-day pump requirement. Some institutions may use alternative vancomycin trough goals, but efficacy data implementing this strategy are lacking. Data published in 2023 suggest that trough concentrations <12 mg/mL have a high incidence of AUC discordance and may not be appropriate when using trough-based monitoring goals [25]. In addition, the operational burden of trough-based monitoring remains, as vancomycin concentration and administration time must be verified for proper assessment of both trough-based and bayesian modeling strategies.

Strengths of the current study include congruency during multiple time periods. Findings in the initial pharmacist-driven AUC cohort were similar to those in the more recent pharmacist-driven AUC cohort, which suggest consistent benefit with use of bayesian modeling. Our study does have limitations. It was a single-center study, and analysis was limited to data documented in the EMR. Patients presenting again for care related to vancomycin or the index infection outside our health system may not have been captured. Our study may also be at risk for recall bias, as vancomycin administration timing was described by the patient and could not be independently verified, which may decrease the accuracy of bayesian calculations or trough interpretations. However, since efficacy outcomes were similar between groups, it is unlikely that this significantly affected our findings. Finally, our data include time before and after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. The trough-based and AUC 2 cohorts both occurred after the public health emergency was declared. Given that the outcomes between AUC 1 and AUC 2 cohorts were consistent, the impact on our study findings was likely minimal.

In conclusion, a pharmacist-driven vancomycin monitoring program using bayesian modeling resulted in significantly less nephrotoxicity development without compromising clinical efficacy. In addition, bayesian modeling improved flexibility in the timing of serum concentration assessments, resulting in fewer unusable serum concentrations. This study supports using bayesian AUC modeling in outpatient vancomycin therapy as a valuable tool for OPAT programs.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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