Original Research

Implementing AUC Monitoring in a Pharmacist-Managed Vancomycin Dosing Protocol: A Retrospective Cohort Study

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Abstract

Background
Consensus guidelines on the therapeutic drug monitoring of vancomycin published in 2020 recognize that using the calculated area-under-the-curve (AUC) to guide dosing maximizes clinical efficacy and minimizes risk when compared to traditional trough-based dosing. The purpose of this study was to determine whether AUC monitoring results in reduced acute kidney injury (AKI) rates in adult patients receiving vancomycin for all indications.

Methods
In this study, patients 18 years or older who received pharmacist-managed vancomycin therapy were selected using pharmacy surveillance software from 2 timeframes. Patients were excluded if they received less than 48 hours of therapy or had unstable renal function or hemodialysis at baseline. The primary outcome measured was the incidence of AKI in each group of patients.

Results
Data were collected for 121 patients in each group. Concomitant nephrotoxins used in each group, as well as the sources of infection, were similar between groups. AUC monitoring did not result in a significant decrease in AKI rate (16.5% in AUC group, 14.9% in trough group; $P = .61$). However, patients who received AUC monitoring were more likely to be therapeutic at first follow-up compared to the trough monitoring group (43.2% in AUC group, 33.9% in trough group; $P = .03$). AUC monitoring also resulted in lower trough levels and total daily doses, with no difference in mortality or length of stay.

Conclusion
AUC monitoring did not result in an observed decrease in AKI rate. Despite this, the AUC monitoring protocol was effective at reaching the goal AUC of 400-600 mg*hour/L and did not increase mortality or length of stay.

Keywords
vancomycin; pharmacokinetics; anti-bacterial agents; anti-bacterial agents/administration & dosage; anti-bacterial agents/pharmacokinetics; area under curve; acute kidney injury; drug monitoring

Background
Vancomycin is a tricyclic glycopeptide antibiotic used to treat gram-positive infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA). It targets gram-positive bacteria by inhibiting cell wall synthesis, resulting in cell death.[1] Both in-vitro and mouse thigh infection models have demonstrated that the bactericidal effect of vancomycin most strongly correlates to the 24-hour area-under-the-curve

(AUC) to minimum inhibitory concentration (MIC) ratio.[2] Studies of MRSA pneumonia found that those with an AUC/MIC value greater than 400 mg × hour/L had a higher likelihood of clinical success compared to lower AUC/MIC values.[2]

There are 2 methods for calculating vancomycin AUC. One method utilizes 2 vancomycin levels drawn at a steady state. A peak level is drawn 1 to 2 hours after the infusion is complete and a trough level is drawn prior to the next dose.[3] This method allows for patient-specific kinetics, but is more labor intensive. The second method, called Bayesian modeling, utilizes population data to calculate AUC from 1 or more vancomycin levels. While Bayesian modeling avoids the increased cost and labor of drawing 2 levels, the software is more expensive and not available at all institutions.[4]

Therapeutic drug monitoring is necessary because of vancomycin nephrotoxicity. Some studies have found that nephrotoxicity occurred in less than 1% of patients undergoing vancomycin therapy, while others have shown rates as high as 42.6%.[5] The mechanism of nephrotoxicity is attributed to oxidative damage in the proximal tubules.[5] Other factors associated with increased risk of nephrotoxicity include elevated trough concentrations, baseline renal insufficiency, doses greater than 4 g/day, and concomitant nephrotoxins.[5]

The Infectious Diseases Society of America previously recommended a trough level range of 15-20 mg/L as the standard of care to approximate an AUC/MIC ratio above 400 mg × hour/L.[3] A major limitation to using troughs as a surrogate was the interpatient variability in AUC values for each trough level. Calculated AUC values vary because they incorporate peak concentrations that are dependent on a patient's volume of distribution. A pharmacokinetic study showed approximately 50% of the inter-individual variability in the AUC value was not explained by the trough level. Patients could achieve AUC values above 400 mg × hour/L with troughs lower than 15 mg/L, and troughs of 15-20 mg/L could result in AUC values greater than 600 mg × hour/L.[6] This poses a risk to patients, as trough levels greater than 15 mg/L have been shown to have a threefold increased risk of acute kidney injury (AKI).[7] Furthermore, those with AUC values less than 650 mg × hour/L were found to have a lower risk of AKI than those with higher AUC values with an odds ratio (OR) of 0.36 (95% Confidence Interval [CI], 0.23-0.56).[8] Directly monitoring vancomycin AUC is a way to avoid vancomycin nephrotoxicity. A single-center study found significantly reduced AKI incidence after implementing AUC monitoring (hazard ratio, 0.53; 95% CI, 0.35-0.78; P = .002).[9] AUC monitoring was further supported by a meta-analysis that showed a significantly lower AKI rate than trough monitoring (OR, 0.68; 95% CI, 0.46-0.99).[8] Consensus guidelines on therapeutic drug monitoring of vancomycin published in 2020 recognized that using AUC to guide dosing maximizes clinical efficacy compared to traditional trough-based dosing. The new guidelines recommended an AUC/MIC ratio of 400-600 mg × hour/L for patients treated for serious MRSA infections to reduce nephrotoxicity and ensure efficacy.[3]

The 2020 vancomycin guidelines specified AUC monitoring for serious MRSA infections, as they had insufficient evidence to recommend AUC-guided dosing over trough-guided dosing for noninvasive MRSA or other infections.[3] Many patients receive vancomycin for days before a MRSA infection is confirmed. Using the same dosing strategy for all patients receiving vancomycin would simplify therapeutic drug monitoring and prevent therapeutic goals from changing after initiation. The purpose of this study was to determine whether AUC monitoring resulted in reduced AKI rates in all adult patients receiving vancomycin for all indications.

Methods

This study was conducted at HCA Houston Healthcare Kingwood, a community teaching hospital that serves the Northeast area of Houston, Texas. Per hospital policy, vancomycin dosing for adult patients is managed by clinical pharmacists. These clinical pharmacists are responsible for ordering vancomycin doses, ordering labs to monitor therapy, and adjusting daily doses to meet the desired therapeutic goal. Prior to implementation, pharmacists used indication-based trough goals to guide therapy. To align with the 2020 guidelines, the policy was updated to target an AUC of 400-600 mg × hour/L. All vancomycin dosing, monitoring, and adjustments were conducted

by pharmacists using a web-based calculator integrated into pharmacy surveillance software. These calculations used 2 different vancomycin levels collected at, or near, steady state. The first level was collected 1 to 2 hours after the end of the infusion and the second level was collected prior to the next dose. These levels provided a patient-specific volume of distribution and half-life which were used to calculate AUC. Training of nursing, pharmacy, medical, and laboratory staff was conducted over a month-long period before the new policy went live in November 2020.

Design

This single-center, retrospective cohort study was conducted to compare patients who were treated with vancomycin before and after the implementation of AUC monitoring in November 2020. The pre-implementation cohort received the previous standard of trough-based monitoring according to the previous hospital protocol with trough goals determined by the clinical pharmacist according to the indication. A 2-month period between cohorts allowed for training and implementation of the new policy. The post-implementation cohort received AUC-based monitoring according to the new hospital protocol. Data were collected from the electronic health record by the primary investigator. Patients' data were collected and de-identified after discharge. The new vancomycin policy was approved by the hospital's Pharmacy and Therapeutics committee and the research protocol was overseen by and received institutional review board (IRB) exemption from the hospital's IRB committee.

Patient Selection

Patients met inclusion criteria if they were 18 years or older and received pharmacist-managed vancomycin therapy for at least 48 hours. Patients were excluded if they were pregnant, had unstable renal function (defined as those who could not receive regularly scheduled maintenance doses due to advanced chronic kidney disease or AKI at baseline), were receiving hemodialysis at baseline, or did not have any vancomycin levels collected during treatment. Patients who received vancomycin from August 1, 2020, to September 30, 2020, who met inclusion criteria, were included in the pre-implementation cohort. Patients who received vancomycin from December 1, 2020, to January 31, 2021, and met inclusion criteria, were included in the post-implementation cohort.

Outcomes

The primary outcome measure was the incidence of AKI during vancomycin therapy. This was defined as an increase in serum creatinine by 0.3 mg/dL or greater, or 1.5 times baseline, to align with the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) definition.[10] To rule out AKIs unrelated to vancomycin therapy, the increase in serum creatinine had to occur during therapy or within 24 hours of discontinuation. Urine output was not utilized due to inconsistency and infrequency of measurements. Secondary outcomes included the following: incidence of hemodialysis initiation, percentage of patients within AUC goal, total daily vancomycin doses, number of vancomycin levels drawn, percentage of patients within trough goal, calculated AUC, duration of therapy, length of stay, and inpatient mortality. The first follow-up in this study was defined as the first time clinical pharmacists collected and assessed vancomycin levels during therapy.

Additional data were collected regarding the source of infection and concomitant nephrotoxic medications to compare between groups and assess their potential impact. Potential nephrotoxic medications were outlined at the beginning of the study for data collection and included piperacillin/tazobactam, contrast dye, aminoglycosides, and others. However, this list was limited by the time available for data collection. Similarly, standard baseline characteristics were determined at the beginning of the study and are listed in **Table 1**.

Statistics

Statistical analysis was conducted using Microsoft Excel and AcaStat version 2200.5.4. Categorical data were analyzed using chi-square and Fisher's exact tests where appropriate, whereas continuous data were analyzed using two-tailed t-tests and the Mann-Whitney test. *P* values less than .05 were determined to be statistically significant. Based on published AKI rates of 9.7% for trough monitoring and 6.8% for AUC monitoring, the number of patients needed to obtain a statistical power of 80% was determined to be 107 in each group using the Kelsey and Fleiss equations.[8]

Table 1. Patient Baseline Characteristics.

Characteristic	Trough only (n=121)	AUC (n=121)	*P* value
Age in years, mean ± SD	60.3 ± 15.0	59.6 ± 16.6	.73
Elderly, age ≥ 65 (%)	50 (41.3)	53 (43.8)	.58
Weight in kg, mean ± SD	88.4 ± 27.7	89.7 ± 28.3	.72
BMI, mean ± SD	31.0 ± 9.2	30.8 ± 9.9	.86
Obese, BMI ≥ 30 kg/m^2 (%)	60 (49.6)	57 (47.1)	.80
Male, n (%)	59 (48.8)	76 (62.8)	<.002
Number of concomitant nephrotoxins, mean ± SD	1.2 ± 0.9	1.2 ± 1.0	.99
Positive MRSA culture, n (%)	16 (13.2)	22 (18.2)	.11
Positive MRSA nares screen, n (%)	9 (7.4)	17 (14.0)	.04

Abbreviations: AUC = area-under-the-curve; BMI = body mass index; MRSA = Methicillin resistant *Staphylococcus aureus*

Results

Upon completion of data collection, 242 patients were included in the final analysis. Baseline characteristics are summarized in **Table 1**. The AUC group had 14% more male patients than the trough group ($P < .002$). Baseline serum creatinine levels were similar in each group, as well as the lowest and highest recorded serum creatinine levels (**Figure 1**). The sources of infections were similar in each group with no significant differences (**Table 2**). The majority of infections were skin and soft tissue infections, while pneumonia was the second most common source of infection. Patients with unknown sources of infection accounted for 17% of patients, indicating treatment was empiric with no positive cultures. There was no significant difference in the rate of positive MRSA cultures between groups, but the AUC group had significantly more patients with positive MRSA nares screening than the trough group (7.4% in trough group, 14% in AUC group; $P = .04$). Regarding concomitant nephrotoxins, there were no significant differences between groups. The most common nephrotoxic medication administered with vancomycin was piperacillin/tazobactam, followed by contrast dye (**Figure 2**).

AKI occurred in 14.9% of patients in the trough group compared to 16.5% of patients in the AUC group, but this difference was not statistically significant ($P = .61$). The incidence of hemodialysis initiation did not significantly dif-

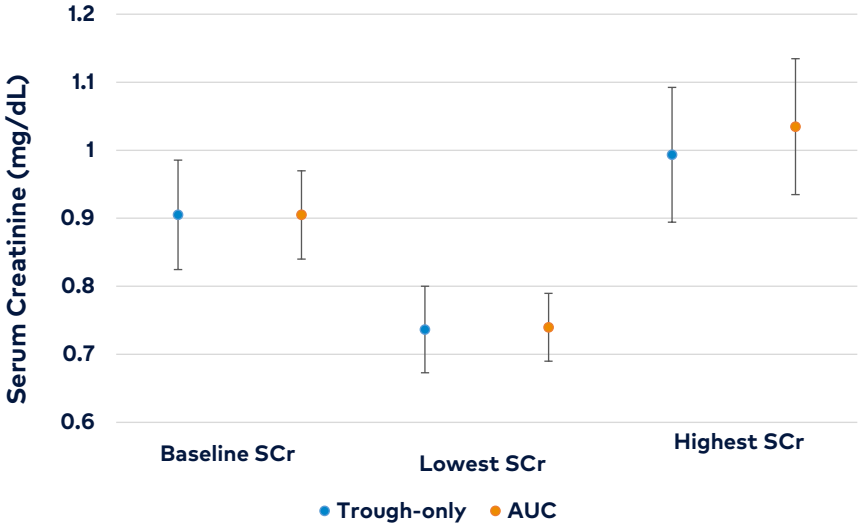

Figure 1. A comparison of serum creatinine measurements shows baseline levels were similar in each group.

Table 2. Suspected or Confirmed Sources of Infection

Source of infection	Trough only (n=121)	AUC (n=121)	*P* value
Skin and Soft tissue, n (%)	42 (34.7)	42 (34.7)	.99
Pneumonia, n (%)	21 (17.4)	28 (23.1)	.13
Unknown, n (%)	25 (20.6)	17 (14.0)	.23
Bone/Joint, n (%)	15 (12.4)	16 (13.2)	.79
Blood, n (%)	13 (10.7)	13 (10.7)	.99
Gastrointestinal, n (%)	3 (2.5)	4 (3.3)	.99
Urinary tract, n (%)	2 (1.7)	0	.5
Central nervous system, n (%)	0	1 (0.8)	.99

fer between groups, neither did the duration of vancomycin therapy, length of stay, or mortality (**Table 3**). At the first follow-up by the clinical pharmacist, patients who received AUC monitoring were more likely to meet their therapeutic goal compared to patients who had trough-based monitoring (43.2% in AUC group, 33.9% in trough group; *P* = .03). Patients who received AUC monitoring had significantly lower initial, final, and average trough levels than patients in the trough group (**Figure 3**). Furthermore, in the AUC group, the average and final AUCs and their 95% confidence interval were within the therapeutic range of 400-600 mg × hour/L (**Figure 4**). A statistically significant reduction in the average total daily dose was observed in the AUC group compared with the trough group (2.4 g versus 2.7 g, *P* = .04). However, AUC monitoring resulted in significantly more lab draws, with an increase in the median by one (*P* < .001).

A secondary analysis was conducted to determine the rate of AKI in patients receiving vancomycin alone versus those receiving vancomycin plus concomitant nephrotoxic medications. The rate of AKI decreased with the addition of other nephrotoxins to vancomycin when compared to vancomycin alone (**Table 4**). Among patients on both vancomycin and piperacillin/tazobactam, there was no significant difference in the incidence of AKI (18% in trough group, 16.9% in AUC group; *P* = .74).

Discussion

Unlike prior studies, AUC monitoring of vancomycin was not associated with a decreased incidence of AKI.[8,9] Implementing AUC monitoring in this study led to significantly lower trough values and total daily doses, but there was no significant difference in the incidence

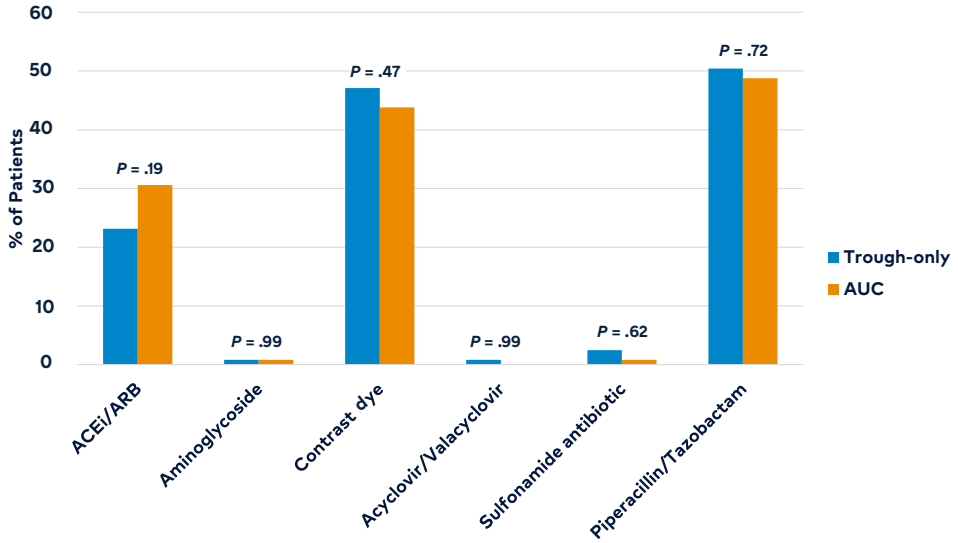

Figure 2. A comparison shows the most common concomittant nephrotoxins administered during vancomycin therapy in each group.

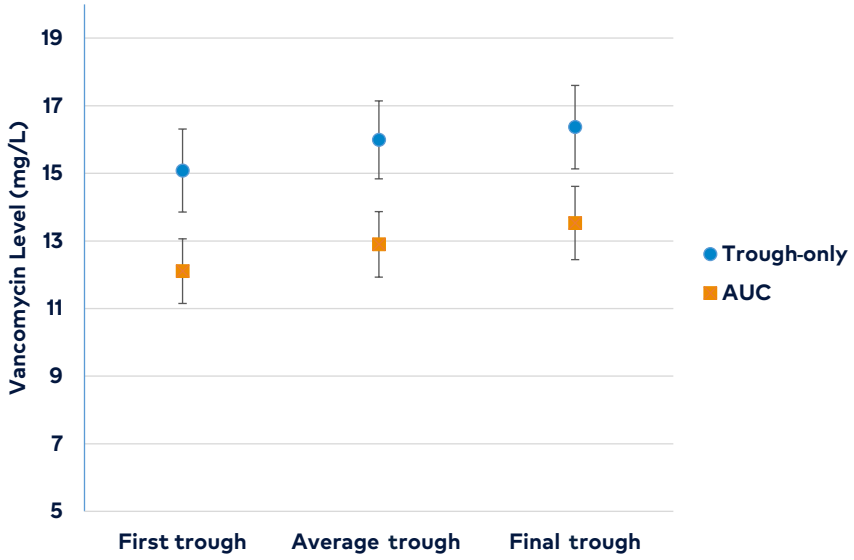

Figure 3. A comparison shows the mean trough levels over the course of therapy in each group.

of AKI. The AUC group had more instances of AKI, but fewer instances of new hemodialysis. Patients only on vancomycin did not have a lower rate of AKI than those receiving concomitant nephrotoxins. Therefore, the AKI rates observed in this study may not have been driven by the medications administered. The most common medication combination was piperacillin/tazobactam and vancomycin. While this was considered a potentially nephrotoxic combination, it did not affect the rate of AKI.

A likely confounding factor was the SARS-CoV-2 virus and COVID-19. The impact of the COVID-19 pandemic was unpredictable at the beginning of the study, so data were not collected regarding COVID-19. Based on data from the Houston Health Department, new COVID-19 cases peaked at 3500 cases per day in January, compared to a peak of 1200 cases per day in August 2020.[11] This information likely correlates with the number of COVID-19 patients hospitalized at this facility during that time. This may explain the increased number of men in the AUC group, as men are at a higher risk of hospitalization for COVID-19 than women.[12] The increased incidence of COVID-19 could have increased the AKI rate in the AUC

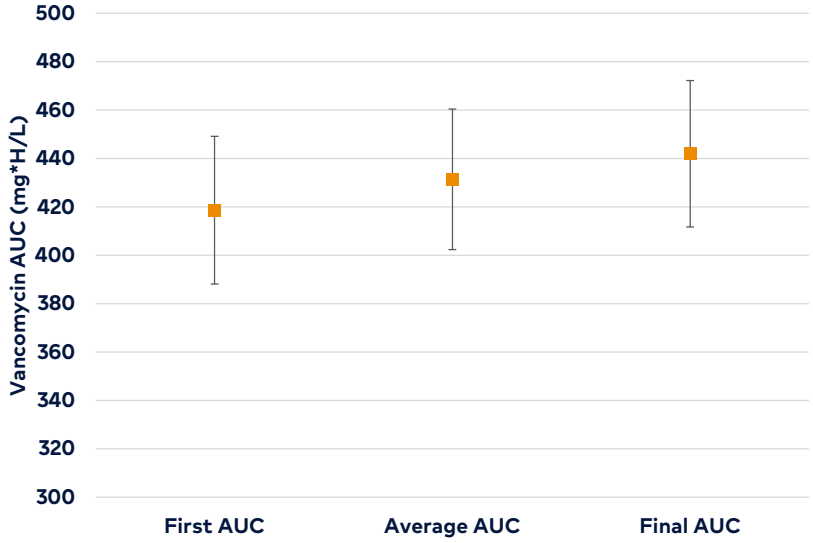

Figure 4. A comparison shows the mean AUC values over the course of therapy in the AUC-monitoring groups.

Table 3. Summary of Outcomes

	Trough only (n=121)	AUC (n=121)	*P* value
Primary outcome			
AKI, n (%)	18 (14.9)	20 (16.5)	.61
Secondary outcomes			
New HD, n (%)	5 (4.1)	2 (1.7)	.45
Therapeutic at first follow-up, n (%)	41 (33.9)	48 (43.2)*	.03
Average total daily dose in grams, mean ± SD	2.7 ± 1.0	2.4 ± 0.9	.04
Number of levels drawn, median ± IQR	2 ± 2	3 ± 2	<.001
Duration of therapy in hours, mean ± SD	105.5 ± 73.3	107.4 ± 65.5	.83
Length of stay in days, median ± IQR	8 ± 9	7 ± 9	.47
Death during admission, n (%)	8 (6.6)	10 (8.3)	.46

* Note: There were only 111 patients in the AUC group for therapeutic at first follow-up due to 10 patients not having AUC calculations.

Abbreviations: AKI = acute kidney injury; HD = hemodialysis

group, as a meta-analysis of 39 studies found AKIs were a common complication in COVID-19 patients, with a pooled odds ratio of 15.47 (95% CI, 20.99-11.4) in patients who expired.[13] The increased risk of AKI due to COVID-19 could have masked the potential benefits of AUC monitoring.

Aside from COVID-19, there are other limitations of this study to consider. AKI rates were higher than those in the study referenced for the power calculation. This meta-analysis had AKI rates of 6.8% and 9.7% in their respective AUC and trough monitoring groups.[8] The KDIGO guidelines were used to define AKI, but this may have resulted in over-reporting AKIs in both groups. Aljefri et al, along with other studies, have commonly defined nephrotoxicity as an increase in serum creatinine of 0.5 mg/L or more.[5,8] The increases in serum creatinine observed in this study may not have been clinically significant or indicative of a true AKI. Another limitation is that patients were screened for certain nephrotoxic medications, but not other nephrotoxic medications like loop diuretics. The dose, route, and duration of these nephrotoxic medications may also affect the rate of AKI, but no data were collected beyond concurrent use. Data on disease severity were not collected; future studies looking at AUC monitoring in critically ill patients may be useful. AUC levels were gathered from pharmacy progress notes and calculations saved on the pharmacy surveillance software. Policy adherence by the clinical pharmacist determining the dosing regimens was not evaluated in this study. Similarly, this study operated under the assumption that each trough level was drawn at the correct time at a steady state. Under this protocol, clinical pharmacists measured AUC at a steady

Table 4. Rate of AKI in Patients Receiving Vancomycin With and Without Other Nephrotoxic Medications

	Trough only (n = 121)	AUC (n = 121)	Combined groups (N = 242)
	AKI, n (%)	**AKI, n (%)**	**AKI, n (%)**
Vancomycin only (n = 58)	6 out of 28 (21.4%)	5 out of 30 (16.7%)	11 out of 58 (19.0%)
Vancomycin + other nephrotoxins (n = 184)	12 out of 93 (12.9%)	15 out of 91 (16.5%)	27 out of 184 (14.7%)

Abbreviation: AKI = acute kidney injury

state. However, measuring AUC and kinetic parameters after the first dose may result in faster attainment of therapeutic goals.[14] This study was not designed to evaluate cost, so a future study may be beneficial to evaluate the financial burden of increased lab draws.

This study also has several strengths. The benefit of AKI reduction with AUC monitoring was evaluated for all patients receiving vancomycin, not just patients with invasive MRSA infections. There were similar proportions of patients in each group that did not have positive MRSA cultures, as well as a majority of patients in each group that were being treated for skin and soft tissue infections. Therefore, this study shows that the IDSA guidelines recommendation on AUC-guided dosing may be safely extended to these patients. This study also evaluated an AUC protocol that utilized 2-level kinetics rather than Bayesian software, showing that it can be successfully implemented without access to specialized software. This study showed that AUC monitoring reduced total daily doses and trough levels, which was also observed in the Detroit Medical Center study.[9] The AUC-guided protocol was effectively implemented, as it resulted in more patients achieving therapeutic goals at the first measurement by clinical pharmacists. This potentially reduces the need for frequent dose adjustments by pharmacists.

Conclusion

This study demonstrated no significant difference in AKI incidence between AUC monitoring and trough monitoring. However, AUC monitoring was found to be effective at reducing total daily doses and trough concentrations while ensuring patients were in the goal range of 400-600 mg × hour/L. Furthermore, the reduced exposure to vancomycin was not accompanied by worse patient outcomes, such as increased length of stay or mortality.

Conflicts of Interest

The author declares that they have no conflicts of interest.

The authors are employees of HCA Houston Healthcare Kingwood, a hospital affiliated with the journal's publisher.

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