Implementation of a Pharmacist-Driven Two-Level AUC-Based Vancomycin Dosing Strategy at a VA Medical Center

by
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ABSTRACT

Background: This project sought to improve patient safety and outcomes by implementing a novel approach to monitor and adjust vancomycin dosages following release of the 2020 consensus vancomycin dosing guidelines. The implementation of vancomycin dosing according to vancomycin AUC concentrations has the potential to reduce associated acute kidney injury by about 50% from previous vancomycin dosing by trough concentrations. The primary outcome was the rate of vancomycin associated acute kidney injury. Secondary outcomes included length of stay, mortality, and desirability of outcome ranking, and pharmacologic outcomes included frequency of target AUC attainment and correlating vancomycin trough values.

Methods: This project assessed vancomycin usage before and after implementation of an AUC-based therapeutic monitoring program. Post data comprised four months following implementation of a vancomycin AUC-based therapeutic monitoring program (November 1st, 2020 to February 28th, 2021) and compared to standard of care in the same time period of the previous year (November 1st, 2019 to February 28th, 2020). Inpatient clinical pharmacy specialists (CPS) were responsible for designing vancomycin regimens using a target 24-hour AUC goal of 400-600 mg*hr/L after the initial dose. Monitoring to estimate the vancomycin AUC, was performed by attaining vancomycin peak and trough levels. The CPS calculated a new vancomycin regimen which was predicted to attain a 24-hour vancomycin AUC level of 400-600 mg*hr/L according to a Microsoft® Excel®-based calculator using first-order pharmacokinetic equations. Data collected in this evaluation included eGFR and serum creatinine levels to stratify patients according the RIFLE and AKIN classifications of acute kidney injury, length of stay, mortality, desirability of outcome ranking, predicted and attained AUC values, and serum trough concentrations.

Results: A total of 408 patients received at least one dose of vancomycin during the pre-implementation period and 602 patients received at least one dose of vancomycin in the post-implementation period. 85 patients in the pre-implementation and 40 patients in the post-implementation period were included in the final analysis. Acute kidney injury (AKI) defined by AKIN and RIFLE criteria occurred in 9-10 (10.5% – 11.6%) and 4-5 (10%-12.5%) of patients in the pre- and post-implementation groups respectively. Acceptable peak and trough vancomycin levels were drawn at steady state for 25 of 39 patients (64%) in the post-implementation group (steady state concentrations were not attained in one patient).

Conclusion: A two-level Microsoft® Excel®-based vancomycin AUC-based calculator did not improve rates of AKI, length of stay, or DOOR outcomes compared to trough-only monitoring. While the AUC calculator is able to appropriately calculate vancomycin AUC, it may be unfeasible to conduct two-level vancomycin AUC monitoring at institutions without around-the-clock CPS coverage to facilitate appropriate peak and trough level draws. A one-level Bayesian approach may allow for more reliable vancomycin AUC-based monitoring in all qualifying patients.

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BACKGROUND

Vancomycin is a glycopeptide antibiotic, first discovered in 1952, which is commonly used as empiric and definitive treatment of infections caused by gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MRSA).[1] To reduce the risk of undesirable adverse events such as nephrotoxicity, while ensuring clinical efficacy, vancomycin requires therapeutic drug monitoring. In 2009, a consensus statement by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) was published recommending therapeutic monitoring of vancomycin via attainment of trough levels of at least 10 mg/L to prevent resistance and 15 to 20 mg/L to treat complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *Staphylococcus aureus*.[2] Since the publication of these recommendations, numerous studies have described an alternative method of therapeutic monitoring to improve the safety and efficacy of vancomycin use.[3-9] As a result of these evaluations, ASHP, IDSA, and SIDP released updated vancomycin monitoring recommendations in 2020.[10]

The updated vancomycin monitoring guidelines recommend attainment of an individualized target area under the curve over minimum inhibitory concentration (AUC/MIC) ratio of 400 to 600 mg*hr/L (assuming vancomycin MIC of 1 mg/L) preferably within the first 24 to 48 hours of therapy in patients with suspected or definitive serious MRSA infections. This method of therapeutic monitoring is recommended to replace the previous method of trough-only monitoring in patients with serious MRSA infections.[10] There are two primary methods of predicting and monitoring AUC concentrations in patients receiving vancomycin as described by Pai and colleagues.[11] One method is utilizing a Bayesian derived software to facilitate the prediction of vancomycin AUC. Bayesian software initially uses estimations of a patient's characteristics such as creatinine clearance and volume of distribution based on population pharmacokinetics. As more patient data is input into the Bayesian software, the software uses pharmacokinetic data from prior patients to create a new pharmacokinetic/pharmacodynamic model; known as the Bayesian prior. Vancomycin therapeutic drug monitoring using Bayesian software allows for the use of a single vancomycin level to determine predictions of patient's characteristics; known as the Bayesian conditional posterior. A key to the Bayesian approach is the utilization of a significant amount of prior vancomycin concentrations collected at different times along the infusion curve. Commercially available software platforms incorporate all previously input concentrations to allow for more accurate AUC prediction. These software platforms also allow for levels to be drawn at any time after vancomycin infusion and not necessarily at steady state.

The second method of conducting vancomycin AUC therapeutic monitoring is the utilization of first-order pharmacokinetic equations. This approach requires two concentrations to be drawn - a post-distributional peak and a traditional trough value during the same dosing interval. Monitoring via this method relies on less assumptions

than the Bayesian approach and provides a more evidence-based prediction of the patient's response. Both approaches result in accurate predictions of vancomycin AUC concentrations, however the differences in clinical practice have not been clearly elucidated.

This evaluation sought to identify the safety, pharmacologic, and patient outcomes following implementation of a novel, two-level, guideline-recommended approach to monitor and adjust vancomycin dosages. Based on previous evaluations, the implementation of pharmacist to dose vancomycin according to estimated vancomycin AUC concentrations has the potential to reduce vancomycin associated acute kidney injury by about 50% from previous standard of care.[3,12]

METHODS

This prospective observational quality improvement project was conducted at the Michael E. DeBakey VA Medical Center (MEDVAMC), an academic medical center affiliated with the Baylor College of Medicine in Houston, Texas. MEDVAMC serves as the primary health care facility for over 130,000 veterans. The hospital's internal medicine service comprises of eleven medical teams led by an attending physician with assistance from resident physicians and medical students. MEDVAMC is also home to a 40 bed spinal cord injury (SCI) unit and offers a variety of surgical services. A clinical pharmacy specialist (CPS) is assigned to each medical, surgical, and SCI team. The CPS rounds with their primary assigned medicine team and completes therapeutic monitoring and medication reviews for both their primary and secondary teams. The CPS is also responsible for therapeutic monitoring of vancomycin and recommending appropriate labs and dosing regimens.

This quality improvement project sought to reduce the instances of risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) and Acute Kidney Injury Network (AKIN) defined (**Tables 1.1 and 1.2**) acute kidney injury (AKI) attributable to vancomycin across the included patient population over four months after implementation of a pharmacist driven vancomycin AUC-based therapeutic monitoring protocol (November 1st, 2020 to February 28th, 2021) as compared to standard of care in the same time period of the previous year (November 1st, 2019 to February 28th, 2020). This evaluation also sought to determine the utility of a two-level Microsoft® Excel®-based vancomycin AUC calculator to accurately predict vancomycin AUC levels.[13,14] Additional aims included assessment of length of stay, duration of vancomycin treatment, and mortality before and after implementation of the protocol.

Implementation of the pharmacist driven AUC based therapeutic monitoring

The inpatient CPSs assigned to internal medicine teams, SCI unit, and surgery teams had the opportunity to opt-in or opt-out of participation in this evaluation following an informational session on August 5, 2020. CPSs who opt-in were responsible for

dosing vancomycin using a target 24-hour AUC goal of 400-600 mg*hr/L for all doses after the initial dose. The initial vancomycin dose may have been placed by the medical teams according to MEDVAMC's antimicrobial dosing guidance which utilizes the patient's weight, creatinine clearance, and severity of illness when determining an appropriate dose. The CPS may have placed the order for the first dose if they are on duty. Education was provided to physicians and medical trainees regarding this evaluation and protocol. They were instructed to place orders for two vancomycin levels to be drawn following the initial dose and when vancomycin reaches steady state. A peak level was to be drawn at least one hour after the end of the infusion, and a trough level was to be drawn 30 minutes prior to the next scheduled dose. The CPS assigned to the patient's team used these observed lab values and patient characteristics to calculate and place orders for a new vancomycin dose and schedule predicted to attain a 24-hour vancomycin AUC level of 400-600 mg*hr/L according to the Microsoft® Excel®-based calculator.

Education was provided to inpatient CPSs regarding vancomycin AUC calculation and the use of the Microsoft® Excel®-based calculator. Equations used to create the calculator may be found in **Appendix A.** A two-month transition period (September - October 2020) was used to complete the education and allowed CPSs to begin implementing this approach in their patients requiring vancomycin. Education to the participating medicine, SCI, and surgery teams occurred simultaneously.

Evaluation of pre- and post-implementation outcomes

Patients receiving vancomycin for greater than 48 hours were included in the pre- and post-implementation analysis. Patients were excluded from analysis if they were admitted to an intensive care unit or community living center, had unstable renal function (CrCl <30 mL/min), were receiving renal replacement therapy, were receiving vancomycin for surgical prophylaxis, or were receiving vancomycin as part of outpatient parenteral antimicrobial therapy. Patients in the post-implementation group must have been under the care of a CPS participating in the vancomycin AUC dosing program.

Previous standard of care was used as the project comparator. Data from a matched timeframe was used in the previous standard of care analysis (from November 1st, 2019 to February 28th, 2020). During this time, patients routinely had their vancomycin dosage adjusted based on steady state trough values. The Veterans Information Systems and Technology Architecture (VISTA) and Computerized Patient Record System (CPRS) were utilized to monitor vancomycin orders, lab values, and other patient characteristics required for to determining appropriate vancomycin therapy. All vancomycin orders were reviewed weekly via retrospective chart review.

STATISTICAL ANALYSIS

This project utilized a pre- and post- method of comparison. The null hypothesis of the primary safety endpoint was that there is no difference between standard of care and the implementation of a pharmacist to dose vancomycin utilizing an AUC approach. Categorical variables were analyzed using Chi SquFischer exact test. Parametric continuous variables were analyzed using the student t-test, and non-parametric continuous variables were analyzed using the Wilcoxon Rank Sum test. Paired t-test was used to assess predicted and attained steady state AUC values. All significance tests were 2-tailed assuming an alpha value less than 5%.

To conduct the desirability of outcomes ranking (DOOR) analysis, patients were assigned a value based on their treatment outcomes and adverse events (**Table 1.3**). This evaluation was made upon discontinuation of antibiotic therapy or death, whichever scenario occurred earlier. Patient's duration of vancomycin therapy was also noted. The product of the outcome value and duration of vancomycin therapy was then be used to calculate the patient's DOOR value. Patients were then ranked according to their DOOR value among their respective cohort. The number of patients in the pre-implementation group with a lower DOOR value was noted for each post-implementation patient. The sum of the number of patients with a lower DOOR value in the post-implementation group vs. the pre-implementation group was divided by the total number of possible pair-wise comparisons to determine the odds ratio. Statistical analyses were performed using STATA® (College Station, TX).

RESULTS

Patients

Of the 408 and 602 patients who received vancomycin during the pre- and post-implementation periods, 85 and 40, respectively, were included in the final analysis. Reasons for exclusion can be found in **Figure 1.1.** Baseline characteristics can be found in **Table 2.1**. Patients in the post-implementation group tended to be younger on average (69 years vs. 62 years) and included more patients from the SCI service. While considered an inpatient unit, patients frequently have extended lengths of stay while admitted to the SCI service. The most common indication for vancomycin was skin and soft tissue infection (SSTI) (28-40%) followed by pneumonia (15-26%). Patients on average received 14 and 16 doses of vancomycin in the pre- and post-implementation group respectively. The average initial total daily dose (TDD) of vancomycin was 2129.4 mg in the pre-implementation group and 2343.8 mg in the post-implementation group. Seven (17.5%) patients received at least one concomitant dose of a nephrotoxic agent post-implementation compared to six (7.1%) patients pre-implementation.

Safety Outcomes

Acute kidney injury (AKI) defined by AKIN and RIFLE criteria occurred in 9-10 (10.5% – 11.6%) and 4-5 (10%-12.5%) of patients in the pre- and post-implementation

groups respectively (**Table 2.2**). Of the eight patients with steady state AUC values greater than 600 mg*hour/L, two patients experienced AKI according to RIFLE criteria. The mean change in serum creatinine was 0.11 ± 0.2 in the pre-implementation group and 0.18 ± 0.5 in the post-implementation group (p=0.297).

Pharmacologic Outcomes

Acceptable peak and trough vancomycin levels were drawn at steady state for 25 of 39 patients (64%) in the post-implementation group (steady state concentrations were not attained in one patient). Of the 25 patients to have vancomycin levels drawn correctly at steady state, 15 (60%) attained the target AUC of 400-600 mg*hr/L upon reaching steady state. Comparatively, of the 80 patients to have vancomycin trough levels appropriately drawn at steady state for the pre-implementation group, 53 (66%) attained target values of 10-20 mcg/mL upon reaching steady state. In patients with appropriately drawn peak and trough levels, the calculator predicted steady state AUC values of 491.1 ± 136.4 and the attained value was 544.4 ± 116.7 (p=0.1232). Average trough levels in the pre-implementation group were 16.59 ± 4.87 and 15.37 ± 4.34 in the post implementation group (p=0.2125). Supratherapeutic trough values (>20 mcg/mL) occurred numerically more frequently in the pre-implementation group 20 of 80 patients (25%) compared to 5 of 34 patients (15%) in the post-implementation group (p=0.3228**). Figures 1.5 and 1.6** demonstrate the correlation of predicted and attained AUC values and attained AUC values and observed trough values.

Patient Outcomes

The median length of stay was nine days in the pre-implementation group compared with eleven days in the post-implementation group (p=0.4335). Median vancomycin duration of therapy was 5 days compared to 5.5 days in the post-implementation group (p=0.3794). Rates of DOOR outcomes were non-significantly different among the two groups. There were a numerically higher number of patients in the post-implementation group who experienced DOOR criteria three, 21 (52.5%) compared to 34 (40%) in the pre-implementation group. The probability of a better DOOR outcome for a randomly selected patient from the post-implementation strategy compared to the pre-implementation strategy is 38.3% (95% confidence interval, 31.3%-45.3%). A probability greater than 50% indicates a meaningful improvement from previous standard of care. Three (3.5%) of patients in the pre-implementation group experienced in-hospital mortality as compared with 1 patient in the post-implementation group which was COVID-19 related.

DISCUSSION

This evaluation shows that the use of a two-level Microsoft® Excel®-based vancomycin AUC-based calculator may not be the most feasible method of assessing AUC in all hospital situations. The results of this evaluation are in contrast with a similarly conducted evaluation by Meng and colleagues demonstrating feasibility of a two-level Microsoft® Excel®-based approach to vancomycin AUC monitoring.[12] While this calculator reasonably predicted AUC-levels, logistical challenges in collecting peak and trough vancomycin levels resulted in AUC calculations being

performed only 62.5% of the time. Of those that had vancomycin levels collected appropriately, 60% achieved target vancomycin AUC attainment. Average steady state trough levels were comparable between the pre- and post-implementation groups. Despite numerically higher instances of supratherapeutic trough levels in the pre-implementation group, rates of AKI were no different in the pre- and post-implementation groups. AUC-based dosing did not improve patient's DOOR outcomes, length of stay, or vancomycin duration of therapy. There were more patients in the post-implementation group receiving care under the SCI service where patients commonly have very extended stays. To account for this, statistical analysis for length of stay and duration of vancomycin therapy were completed using Wilcoxon-Rank Sum test and showed a non-statistically significant difference.

Several limitations were identified during this evaluation. The proportion of patients receiving at least one dose of concomitant nephrotoxic agents was greater in the post-implementation group, 17.5%, compared to 7% in the pre-implementation group. The most common nephrotoxic agent used was piperacillin/tazobactam (57% and 50% respectively). The post-implementation period took place following the onset of the COVID-19 pandemic and changes in institutional policy regarding work-from-home. Work-from-home reduced the CPS's ability to have conversations with bed-side nurses regarding the timing and interpretation of vancomycin administration and lab draws. It is likely that an increased number of patients received vancomycin empirically during this time for unknown pulmonary infection which may ultimately have been viral in nature. One patient in the post-implementation group experienced grade 3 AKI and passed away, however this was unlikely affected by vancomycin administration and brought upon by COVID-19 infection. To assess AKI, the patient's most recent serum creatinine and eGFR prior to vancomycin initiation was compared to the peak serum creatinine and nadir eGFR while receiving vancomycin. The context of AKI and a determination of whether the AKI was directly associated with vancomycin administration was not made. This project assessed the earliest occurrence of steady state vancomycin peak and trough concentrations. It is possible that patients had multiple appropriately drawn concentrations, however data regarding subsequent trough levels and AUC concentrations was not assessed.

During implementation of AUC-based therapeutic monitoring at MEDVAMC, several challenges were identified. At the time of evaluation MEDVAMC had CPS coverage only during the day shift which impacted appropriate vancomycin concentration gathering. MEDVAMC is a teaching hospital with continuously rotating attending physicians, medical fellows, residents, and students. The burden of continuously educating these teams about the AUC-based approach to vancomycin dosing was placed on the team CPS. Communication between pharmacy, physicians, and nurses was crucial in ensuring peak and trough vancomycin levels were drawn successfully and that vancomycin was not held inappropriately based on peak levels. Participating pharmacists found placing nursing text orders in the electronic health record (EHR) which explicitly stated instructions for drawing and interpreting lab values to be a successful method of communication. Despite improvements in communication, without around the clock CPS coverage, two-level AUC-based therapeutic monitoring

proved difficult. In addition to communication issues, it was identified that the times of vancomycin administration and lab collection were not always accurately displayed in the EHR which limits the CPS's ability to accurately predict AUC using the calculator.

Bayesian software would be beneficial in reducing the number of lab draws for nursing staff and patients which would ultimately improve the feasibility of implementing AUC-based dosing at institutions without around the clock CPS coverage. Further studies would need to be conducted to identify the comparability in clinical outcomes between a two-level equation-based approach and a Bayesian approach to vancomycin AUC-based monitoring.

CONCLUSION

This pre- and post-implementation evaluation in a small subset of patients receiving at least two days of vancomycin compared trough-only monitoring with a two-level Microsoft® Excel®-based vancomycin AUC-based calculator. Two matched four-month time periods were used as the pre- and post- implementation periods. The two-level AUC-based monitoring approach proved logistically challenging due to its need for two precisely timed lab draws and interpretation at a facility without around the clock CPS coverage. It was determined that a two-level approach to vancomycin AUC-based monitoring was not able to elicit a reduction in vancomycin associated AKI, vancomycin duration of therapy, or length of stay. Without around the clock CPS coverage, appropriately obtaining both peak and trough vancomycin concentrations at steady state reliably is less feasible than obtaining a single level needed to calculate AUC using the Bayesian approach.

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TABLES

Table 1.1 RIFLE Criteria

Class	Outcome
Risk (1)	↓ GFR >25%
Injury (2)	↓ GFR >50%
Failure (3)	↓ GFR >75%

Table 1.2 AKIN Classification

Class	Outcome
1	↑ SCr ≥ 0.3 mg/dL or ≥ 1.5 to 2x from baseline
2	↑ SCr > 2 to 3x from baseline
3	↑ SCr > 3x from baseline

Table 1.3 DOOR Ranking

Class	Outcome
1	Clinical benefit (resolution of patient symptoms/improved function) without adverse effects (AEs)
2	Clinical benefit with some AEs
3	Survival without clinical benefit or AEs
4	Survival without clinical benefit but with AEs
5	Death

Table 2.1 Baseline Demographic and Clinical Characteristics

	Total (N=125)	Pre-Implementation (n=85)	Post-Implementation (n=40)	P-Value
Age ± SD	67.1 ± 11.7	69.5 ± 10.1	61.9 ± 13.2	0.0005
Male	124 (99%)	84 (98.8%)	40 (100%)	1.00
Weight (kg) ± SD	87.0 ± 24.3	85.5 ± 26.2	90.2 ± 19.8	0.3099
Height (cm) ± SD	178.6 ± 8.2	178.2 ± 8.7	179.4 ± 7.2	0.4641
Body Mass Index (kg/m^2) ± SD	27.3 ± 7.5	26.9 ± 8.2	28.0 ± 5.6	0.4625
Serum Creatinine (mg/dL) ± SD	1.13 ± 0.4	1.13 ± 0.4	1.12 ± 0.7	0.0339

eGFR (mL/min/1.73m^2) ± SD	93.9 ± 51.4	83.1 ± 37.6	116.9 ± 67.4	0.0005
Initial Vancomycin TDD (mg) ± SD	2198 ± 745.5	2129.4 ± 771.1	2343.8 ± 673.9	0.1343
Initial Vancomycin TDD (mg/kg) ± SD	25.8 ± 8.7	26.3 ± 9.6	26.3 ± 9.6	0.6945
Vancomycin Doses Received ± SD	14.5 ± 18.6	13.9 ± 19.32	15.88 ± 16.98	0.5775
Treating Service				
Medicine	85 (68%)	66 (77.7%)	19 (47.5%)	0.0011
SCI	19 (15.2%)	6 (7.1)	13 (32.5%)	0.0008
Orthopedic Surgery	11 (8.8%)	4 (4.7%)	7 (17.5%)	0.0365
Vascular Surgery	6 (4.8%)	6 (7.1%)	0 (0%)	0.1755
Urologic Surgery	2 (1.6%)	1 (1.2%)	1 (2.5%)	0.5394
Plastic Surgery	1 (0.8%)	1 (1.2%)	0 (0%)	1.00
Cardiothoracic Surgery	1 (0.8%)	1 (1.2%)	0 (0%)	1.00
General Surgery	1 (0.8%)	1 (1.2%)	0 (0%)	1.00
Indication				
SSTI	40 (32%)	24 (28.2%)	16 (40%)	
Pneumonia	28 (22.4%)	22 (25.9%)	6 (15%)	
Osteomyelitis	22 (17.6%)	16 (18.8%)	6 (15%)	
Bacteremia	14 (11.2%)	9 (10.59%)	5 (12.5%)	
Septic Arthritis	5 (4%)	3 (3.5%)	2 (5%)	
Abscess	4 (3.2%)	3 (3.5%)	1 (2.5%)	
Empiric	3 (2.4%)	2 (2.4%)	1 (2.5%)	
Urinary Tract Infection	3 (2.4%)	3 (3.5%)	0 (0%)	
Endocarditis	2 (1.6%)	1 (1.2%)	1 (2.5%)	
Febrile Neutropenia	2 (1.6%)	1 (1.2%)	1 (2.5%)	
Prosthetic Joint Infection	2 (1.6%)	1 (1.2%)	1 (2.5%)	

Table 2.2 Results

	Pre-Implementation	Post Implementation	P-Value	95% CI
Safety				
Nephrotoxicity (Any Grade)	10 (11.8%)	5 (12.5%)	1	
AKIN 1	8 (9.41%)	2 (5%)	0.4997	
AKIN 2	1 (1.2%)	1 (2.5%)	0.5394	
AKIN 3	0 (0%)	1 (2.5%)	0.32	
RIFLE 1	9 (10.6%)	3 (7.5%)	0.7503	
RIFLE 2	1 (1.2%)	1 (2.5%)	0.5394	
RIFLE 3	0 (0%)	1 (2.5%)	0.32	
Nephrotoxic Agents	6 (7.1%)	7 (17.5%)	0.1131	
Mean Change in SCr ± SD	0.11 ± 0.20	0.18 ± 0.5	0.297	-0.19 to 0.06
Mean %Change in Scr ± SD	11% ± 21%	24.6% ± 80%	0.1448	-0.32 to 0.05
Mean % Change in eGFR ± SD	10% ± 13%	12.3% ± 18%	0.3524	-0.08 to 0.03
Pharmacologic				
Target Vancomycin AUC Attainment	N/A	15 (60%) n=25		
Trough Levels ± SD	16.59 ± 4.9	15.4 ± 4.3	0.2126	-0.70 to 3.13
Supratherapeutic trough levels (>20mcg/mL) at steady state	20 (25%) n=80	5 (14.7%) n=34	0.3228	
Predicted vs Attained steady state AUC	**Predicted** 491.2 ± 136.4	**Attained** 544.4 ± 116.7	0.1232	-121.92 to 15.52
Outcomes				
Median Length of Stay (Days) (IQR)	9 (6 to 19)	11 (6 to 38)	0.4319	
Median Vancomycin Duration (Days) (IQR)	5 (3 to 7)	5.5 (3 to 9.25)	0.3794	
In-Hospital Mortality	3 (3.5%)	1 (2.5%)	1	
Pharmacy Intervention	10 (11.8%)	17 (42.5%)	0.0003	
Door Criteria				
1	42 (49.4%)	15 (37.5%)		
2	4 (4.7%)	1 (2.5%)		
3	31 (36.5%)	21 (52.5%)		
4	5 (5.9%)	2 (5%)		
5	3 (3.5%)	1 (2.5%)		

FIGURES

Figure 1.1 Inclusion Flow Diagram

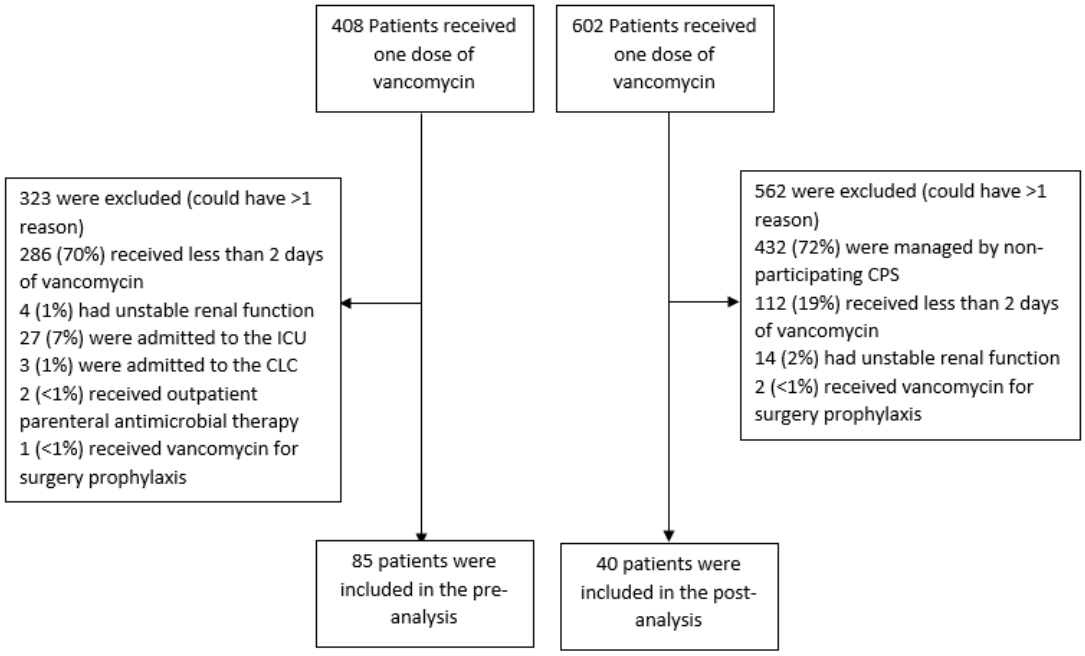


Figure 1.2 Rates of AKI (AKIN)

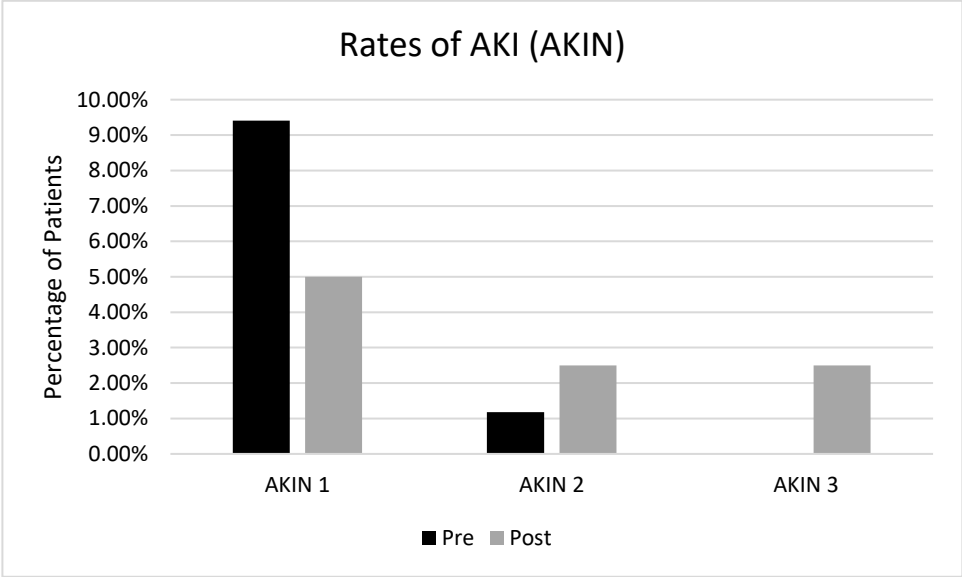


Figure 1.3 Rates of AKI (RIFLE)

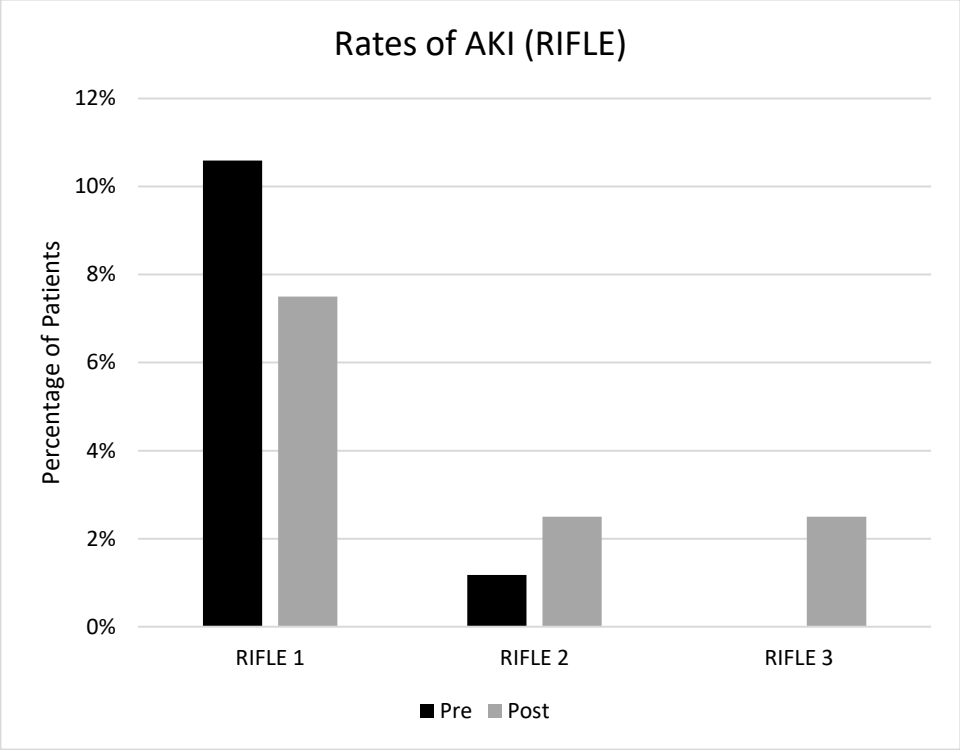


Figure 1.4 DOOR Criteria Outcomes

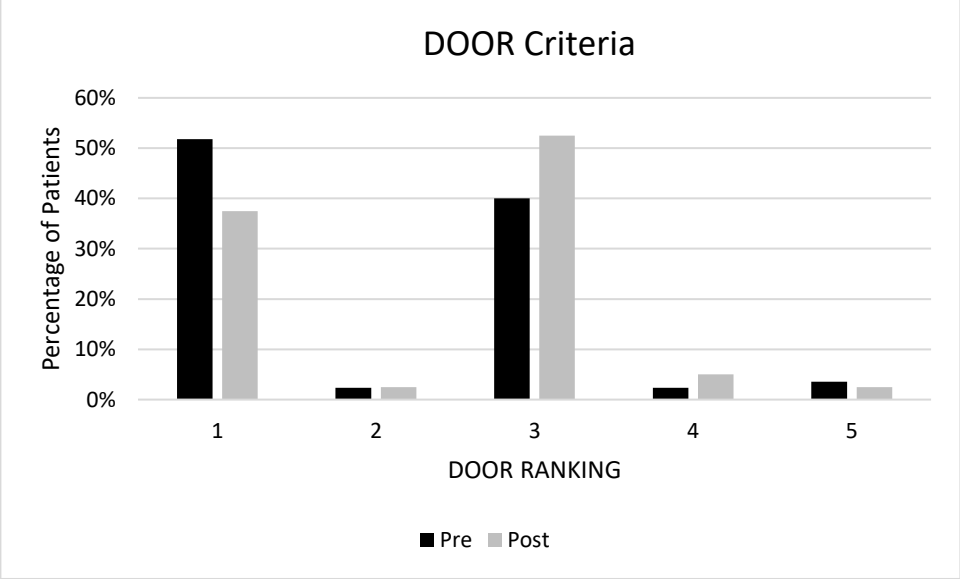


Figure 1.5 Predicted vs. Attained AUC at Steady State

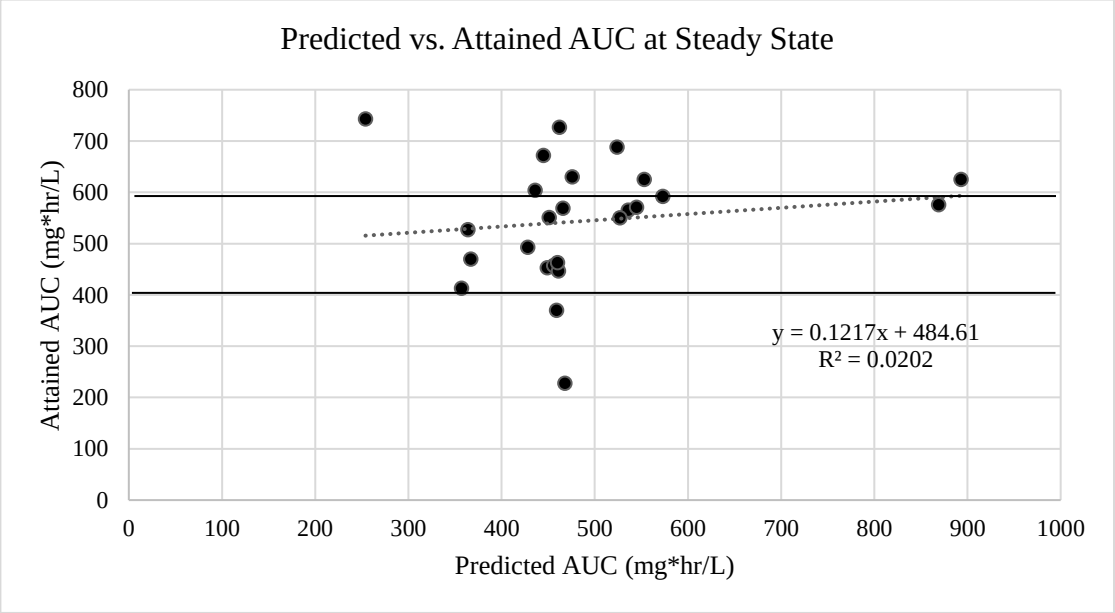
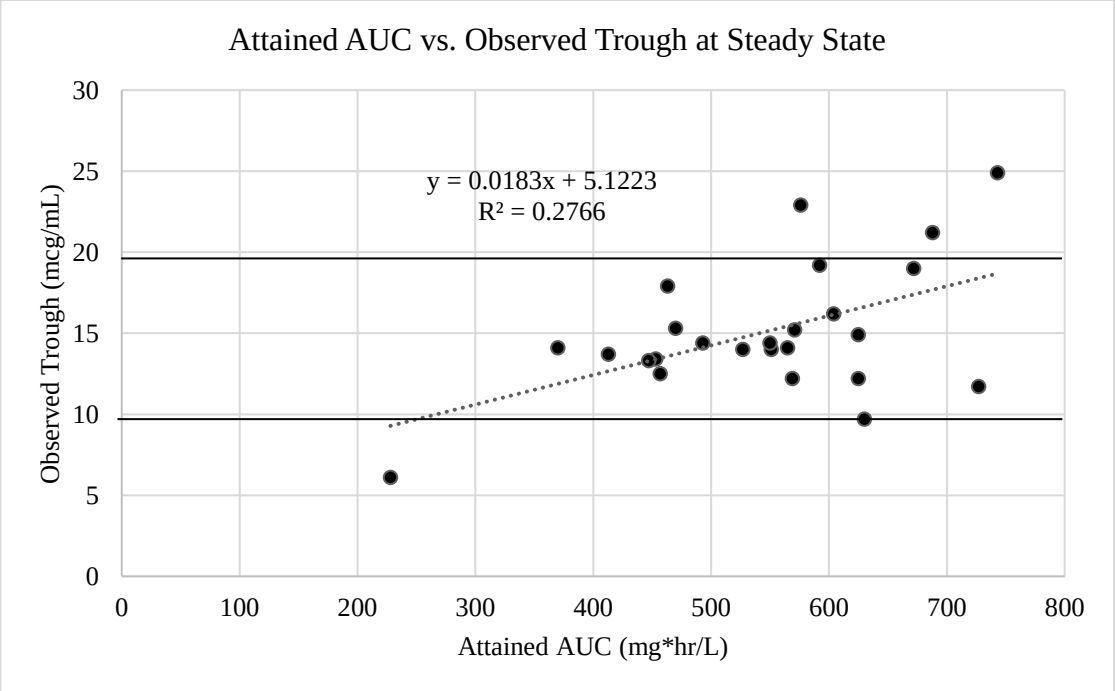


Figure 1.6 Attained AUC vs. Observed Trough at Steady State



APPENDIX A: VANCOMYCIN AUC CALCULATIONS

Initial Empiric Calculator

1. Determine Dosing Weight and Calculate Creatinine Clearance

2. Calculate Body Mass Index (BMI)

$$BMI = \frac{\text{(Actual Body Weight (ABW) in kg)}}{(\text{Height in inches}/39.37)^2}$$

   a. If BMI < 30 kg/m^2, vancomycin elimination rate constant to be estimated using the Matzke equation[13]:

      - Volume of Distribution (V_d)
        V_d = 0.8 x ABW
        Population V_d Estimate of 0.8 based on BMI < 30 kg/m^2

      - Elimination rate constant (k_e): $k_e = (0.00083 + CrCl) + 0.0044$

      - Vancomycin Clearance (Cl): $Cl = V_d \times k_e$

   b. If BMI ≥ 30 kg/m^2, vancomycin clearance to estimated using the Crass equation[14]:

      - Volume of Distribution (V_d)
        V_d = Population V_d Estimate based on BMI x ABW (kg)

BMI (kg/m^2)	**Population V_d Estimate (L/kg)**
<30	0.8
30-39	0.73
40-49	0.57
>50	0.47

      - Vancomycin Clearance (Cl):
        $Cl = 9.656 – (0.078 \times AGE) – (2.009 \times SCr) \times SEX + (0.04 \times ABW^{0.75})$
        AGE in years, SCr in mg/dL, SEX: 1 if male and 0 if female

      - Elimination rate constant (k_e): $k_e = Cl / V_d$

3. Calculate Vancomycin Loading Dose (LD): LD = V_d x Desired Peak
   (Desired Peak: 30-40 mcg/mL)
   All Loading Doses will be capped at a maximum vancomycin dose of 2500mg

4. Calculate Dosing Interval (τ): $\tau = (-1/k)$ x ln(Desired Trough/Desired Peak) (Desired Trough: 10-20 mcg/mL)

5. Calculate Percent Eliminated: Percent Eliminated = $1-e^{-k\tau}$

6. Calculate Vancomycin Maintenance Dose (MD): MD = LD x Percent Eliminated

7. Calculate the Predicted C_{max}:
   $$Predicted\ C_{max} = \frac{(MD/t) \times (1-e^{-kt})}{V_d \times k \times (1-e^{-k\tau})}$$
   t = infusion time of the MD

8. Calculate the Predicted C_{min}:
   $$Predicted\ C_{min} = Predicted\ C_{max} \times e^{-k(\tau-t)}$$
   t = infusion time of the MD

9. Calculate the predicted AUC with dosing regimen:
   $AUC_{infusion}$ = (*Predicted* C_{max} + *Predicted* C_{min})/2 x t (where t = infusion time of the MD)
   $AUC_{elimination}$ = (*Predicted* C_{max} - *Predicted* C_{min})/k
   AUC_{0-24} = ($AUC_{infusion}$ + $AUC_{elimination}$) x ($24/\tau$)

10. Check estimated new vancomycin dosing regimen to ensure achievement of a predicted C_{min} between 10-20 mcg/mL and an estimated AUC_{0-24} between 400-600 mg*hr/L

Vancomycin AUC Dosing Equations after the First Dose

1. Calculate the elimination rate (k):
   $k = [\ln(C_1/C_2)]/(t_2 - t_1)$
   C_1 and t_1 are the vancomycin concentration and time drawn of vancomycin level 1
   C_2 and t_2 are the vancomycin concentration and time drawn of vancomycin level 2

2. Calculate the half-life ($t_{1/2}$): $t_{1/2} = \ln(2)/k$

3. Calculate the maximum vancomycin concentration (C_{max}):
   $C_{max} = C_1/(e^{-k(\Delta T)})$
   ΔT = time between C_1 and the end of the vancomycin infusion

4. Calculate the minimum vancomycin concentration (C_{min}):
   $C_{min} = C_{max}(e^{-kt})$
   Where t can be estimated as 8, 12, 24, or 48 hours to estimate the patient's clearance of vancomycin and when it would be appropriate to re-dose vancomycin

5. Calculate the volume of distribution (V_d):

V_d = (Dose/Infusion Time) x (1-e^{-kt})/(k x C_{max})
Dose = Initial Dose given (Loading Dose if indicated)
t = infusion time of the Initial Dose

6. Calculate the vancomycin clearance (*Cl*): $Cl = k \times V_d$

7. Calculate the total daily dose of vancomycin (TDD):
   TDD = Cl x AUC_{goal}
   AUC_{goal} = 400-600 (use 500 in calculations)

8. Calculate the dosing interval (τ):
   τ = estimated by rounding $t_{1/2}$ up to the nearest whole interval (i.e. 8, 12, 24 or 48 hours)

9. Calculate the Maintenance Dose (MD): MD = TDD/(24/τ)

10. Calculate the Predicted C_{max}: *Predicted* C_{max} = (MD/ V_d)/(1-$e^{-k\tau}$)

11. Calculate the Predicted C_{min}:
    Predicted C_{min} = *Predicted* C_{max} x $e^{-k(\tau-t)}$
    t = infusion time of the MD

12. Calculate the predicted AUC with dosing regimen:
    $AUC_{infusion}$ = (*Predicted* C_{max} + *Predicted* C_{min})/2 x t (where t = infusion time of the MD)
    $AUC_{elimination}$ = (*Predicted* C_{max} - *Predicted* C_{min})/k
    AUC_{0-24} = ($AUC_{infusion}$ + $AUC_{elimination}$) x (24/τ)

13. Check estimated new vancomycin dosing regimen to ensure achievement of a predicted C_{min} between 10-20 mcg/mL and an estimated AUC_{0-24} between 400-600 mg*hr/L

Vancomycin AUC Dosing Equations at Steady State

1. Calculate the elimination rate (k): $k = [\ln(C_{ss,\,peak}/C_{ss,\,trough})]/(T')$
   $C_{ss,\,peak}$ = vancomycin concentration of Vancomycin Level 1 (peak level at steady state)
   $C_{ss,\,trough}$ = vancomycin concentration of Vancomycin Level 2 (trough level at steady state)
   T' = subtract the time difference between the two vancomycin levels from τ (interval)

2. Calculate the half-life ($t_{1/2}$): $t_{1/2} = \ln(2)/k$

3. Calculate the maximum vancomycin concentration (C_{max}):$C_{max} = C_{ss,\,peak}/(e^{-kt'})$

t' = time between $C_{ss,\ peak}$ as drawn and the end of the vancomycin infusion

4. Calculate the minimum vancomycin concentration (C_{min})
   $C_{min} = C_{ss,\ trough}(e^{-kt'})$
   t' = time between $C_{ss,\ trough}$ as drawn and true C_{min}

5. Assess if AUC is within goal range (between 400-600 mg*hr/L) and C_{min} between 10-20 mcg/mL on current vancomycin dosing regimen
   $AUC_{infusion} = (C_{max} + C_{min})/2 \times t$ (where t = infusion time)
   $AUC_{elimination} = (C_{max} - C_{min})/k$
   $AUC_{0\text{-}24} = (AUC_{infusion} + AUC_{elimination}) \times (24/\tau)$

6. If current vancomycin dosing regimen is <u>NOT</u> at the AUC or C_{min} goal range:

   a. Calculate the volume of distribution (V_d)
      V_d = (Maintenance Dose/t) x $(1\text{-}e^{-kt})/\{k(C_{max} - [C_{min} \times e^{-kt}])\}$
      t = infusion time

   b. Calculate the vancomycin clearance (Cl): $Cl = k \times V_d$

   c. Calculate the vancomycin total daily dose (TDD):
      TDD = $Cl \times AUC_{goal}$
      AUC_{goal} = 400-600 (use 500 in calculations)

   d. Calculate the dosing interval (τ)
      τ = estimated by rounding $t_{1/2}$ up to the nearest whole interval (i.e. 8, 12, 24 or 48 hours)

   e. Calculate the maintenance dose (MD): MD = TDD/(24/τ)

   f. Calculate the predicted C_{max}: *Predicted* C_{max} = (MD/ V_d)/$(1\text{-}e^{-k\tau})$

   g. Calculate the predicted C_{min}: *Predicted* C_{min} = *Predicted* $C_{max} \times e^{-k(\tau\text{-}t)}$
      t = infusion time

   h. Calculate the predicted AUC with dosing regimen
      $AUC_{infusion} = (Predicted\ C_{max} + Predicted\ C_{min})/2 \times t$
      (where t = infusion time)
      $AUC_{elimination} = (Predicted\ C_{max} - Predicted\ C_{min})/k$
      $AUC_{0\text{-}24} = (AUC_{infusion} + AUC_{elimination}) \times (24/\tau)$

   i. Check estimated new vancomycin dosing regimen to ensure achievement of a predicted C_{min} between 10-20 mcg/mL and an estimated $AUC_{0\text{-}24}$ between 400-600 mg*hr/L