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BAYESIAN-DERIVED VANCOMYCIN AUC24H THRESHOLD FOR NEPHROTOXICITY IN SPECIAL POPULATIONS

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BAYESIAN-DERIVED VANCOMYCIN AUC_{24H} THRESHOLD FOR NEPHROTOXICITY IN SPECIAL POPULATIONS

Abstract

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A Bayesian-derived 24-hour area under the concentration-time curve over minimum inhibitory concentration from broth microdilution (AUC_{24h}/MIC_{BMD}) ratio of 400 to 600 is recommended as the new monitoring parameter for vancomycin to optimize efficacy and minimize nephrotoxicity. The AUC_{24h} threshold of 600 mg*h/L for nephrotoxicity was extrapolated from studies that assessed the general population. It is unclear if this upper threshold is consistent or varies when used in special populations such as critically ill patients, obese patients, patients with preexisting renal disease, and patients on concomitant nephrotoxins.

The purpose of this study is to investigate the generalizability of the proposed vancomycin AUC_{24h} threshold of 600 mg*h/L for nephrotoxicity. The objective is to determine the optimal Bayesian-derived AUC_{24h} threshold to minimize vancomycin-associated nephrotoxicity in special populations such as critically ill patients, obese patients, patients with preexisting renal disease, and patients on concomitant loop diuretics, ACEIs, ARBs, NSAIDs, aminoglycosides, piperacillin-tazobactam, and IV contrast dyes.

The study design is a single-center, retrospective cohort study. For each patient, nephrotoxicity was assessed and the Bayesian-derived AUC_{24h} was estimated. Using classification and regression tree (CART) analysis, the AUC_{24h} threshold for nephrotoxicity was determined for each special population that had at least ten nephrotoxic patients. The predictive

performances (e.g., positive predictive value [PPV], negative predictive value [NPV], sensitivity, specificity, and area under the receiver operating characteristic [ROC] curve) of each CART-derived threshold were then compared to the guideline threshold's predictive performances. PPV and sensitivity were given greater weight when comparing the thresholds.

Of the 336 patients, 29 (8.6%) nephrotoxic patients were observed after initiating vancomycin. Among the special populations of interest, critically ill patients, obese patients, patients with preexisting renal disease, and patients on concomitant loop diuretics included at least ten nephrotoxic patients and thus were further analyzed to determine the CART-derived AUC_{24h} thresholds. The CART-derived AUC_{24h} thresholds were 544 mg*h/L for critically ill patients (n=116), 586 mg*h/L for obese patients (n=111), 539 mg*h/L for patients with preexisting renal disease (n=54), and 543 mg*h/L for patients on concomitant loop diuretics (n=126). Compared to the guideline threshold of 600 mg*h/L, the CART-derived thresholds for critically ill patients, patients with preexisting renal disease, and patients on concomitant loop diuretics had comparable PPVs but significantly higher sensitivities. On the other hand, the CART-derived threshold for obese patients did not have a significantly different PPV, NPV, sensitivity, specificity, and area under the ROC curve.

For critically ill patients, patients with preexisting renal disease, and patients on concomitant loop diuretics, a lower vancomycin AUC_{24h} threshold for nephrotoxicity such as 544 mg*h/L, 539 mg*h/L, and 543 mg*h/L, respectively, may be considered to minimize the risk of nephrotoxicity. On the other hand, this study supports the continued use of the guideline threshold of 600 mg*h/L to minimize the risk of nephrotoxicity in obese patients.

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ACEI	Angiotensin-converting enzyme inhibitor
AKI	Acute kidney injury
aOR	Adjusted odds ratio
APACHE	Acute Physiology and Chronic Health Evaluation
ARB	Angiotensin II receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
ASHP	American Society of Health-System Pharmacists
AUC	Area under the concentration-time curve
AUC/MIC	Area under the concentration-time curve over minimum inhibitory concentration ratio
BMD	Broth microdilution
BMI	Body mass index
CART	Classification and regression tree
HR	Hazard ratio
IDSA	Infectious Diseases Society of America
ICU	Intensive care unit
IQR	Interquartile range
IRB	Institutional Review Board
IV	Intravenous
IVDU	Intravenous drug users
KDIGO	Kidney Disease: Improving Global Outcomes
MIC	Minimum inhibitory concentration

MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NPV	Negative predictive value
NSAID	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PD	Pharmacodynamics
PK	Pharmacokinetics
PIDS	Pediatric Infectious Diseases Society
PPV	Positive predictive value
ROC	Receiver operating characteristic
RR	Relative risk
SCr	Serum creatinine
SD	Standard deviation
SIDP	Society of Infectious Diseases Pharmacists
SJGH	San Joaquin General Hospital
SSTI	Skin and soft tissue infections
UOP	University of the Pacific
V_d	Volume of distribution

CHAPTER 1: INTRODUCTION

Background

Vancomycin is a bactericidal glycopeptide antibiotic that remains a mainstay of treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) and other severe gram-positive infections.[1,2] When given intravenously, vancomycin demonstrates characteristics of a dose-response and dose-toxicity relationship with a narrow therapeutic index which warrants careful dosing and monitoring of the antibiotic.

Previously published vancomycin therapeutic monitoring consensus guidelines recommended trough concentrations as a surrogate marker for the 24-hour area under the concentration-time curve over minimum inhibitory concentration (AUC_{24h}/MIC) ratio due to a history of difficulty in obtaining multiple vancomycin concentrations and subsequently calculating the area under the concentration-time curve over 24 hours (AUC_{24h}).[1] However, an enhanced method of using Bayesian software programs has been shown to generate accurate and reliable estimates of the AUC_{24h}. Additionally, studies have shown a high degree of interindividual variability between a trough concentration and its respective AUC_{24h}.[9] A simulation of 5,000 vancomycin concentration versus time profiles derived from administering 1,000 milligrams every eight hours examined the relationship between trough concentrations and AUC_{24h} values.[3] In the study, trough concentrations correlated with less than 50% of the AUC_{24h} values (R^2=0.409). Trough concentrations are suspected to be poor surrogate markers for AUC_{24h} values as a trough concentration is a single exposure point after a dose is administered while the AUC_{24h} represents the cumulative drug exposure over 24 hours. Furthermore, no link

between treatment success and vancomycin trough concentrations was demonstrated throughout the entire trough continuum.[3]

On the other hand, with high vancomycin concentration targets, specifically 15 to 20 mg/L, there is a considerable concern for unnecessarily high AUC_{24h} values that can put patients at an increased risk of vancomycin-associated nephrotoxicity.[4] Compared to trough-based monitoring, studies have shown that AUC_{24h}-based monitoring significantly decreased the incidence of vancomycin-associated nephrotoxicity.[5,6] In a retrospective, quasi-experimental study, Finch et al. assessed 546 patients dosed using trough concentrations versus 734 patients dosed using AUC_{24h}.[6] They determined that AUC_{24h}-based monitoring was associated with a significantly lower incidence of vancomycin-associated nephrotoxicity (OR, 0.52; 95% CI, 0.34-0.80; p=0.003). Cox proportional hazards regression also revealed similar results (hazard ratio [HR], 0.53; 95% CI, 0.35-0.78; p=0.002). Moreover, Neely et al. conducted a prospective observational study consisting of 252 patients and compared trough-based monitoring in the first year versus AUC_{24h}-based monitoring in the second and third year.[7] Nephrotoxicity occurred in 8% of the patients in the first year and occurred in 0% and 2% of the patients in the second and third year, respectively. Compared to AUC_{24h}-based monitoring, trough-based monitoring had significantly higher rates of trough concentrations greater than 15 mg/L (p<0.001) and vancomycin-associated nephrotoxicity (p=0.01).

Over the past decade, trough-based monitoring for vancomycin has been well integrated into practice despite limited evidence on the clinical benefits of maintaining trough concentrations between 15 to 20 mg/L for serious MRSA infections. However, in March 2020, the American Society of Health-System Pharmacists (ASHP), Infectious Diseases Society of America (IDSA), the Pediatric Infectious Diseases Society (PIDS), and the Society of Infectious

Diseases Pharmacists (SIDP) published an updated vancomycin therapeutic monitoring consensus guideline that recommends AUC_{24h}-based monitoring over trough-based monitoring for patients with suspected or definitive serious MRSA infections.[4] Due to the guideline's updated recommendation, more clinicians and hospital institutions are in the midst of transitioning or expected to transition to AUC_{24h}-based monitoring for vancomycin.

Introduction to Research

The 2020 ASHP/IDSA/PIDS/SIDP updated vancomycin monitoring guideline no longer recommends trough-based monitoring with a target of 15 to 20 mg/L for patients with serious MRSA infections.[4] Additionally, it recommends a Bayesian-derived AUC_{24h}/MIC from broth microdilution (AUC_{24h}/MIC_{BMD}) ratio of 400 to 600, as the new optimal pharmacokinetics (PK) and pharmacodynamics (PD) target for vancomycin. Rybak et al. concluded that AUC_{24h}-based monitoring using an AUC_{24h}/MIC_{BMD} ratio of 400 to 600 optimizes clinical efficacy and minimizes nephrotoxicity risk in patients with serious MRSA infections such as bacteremia, pneumonia, and osteomyelitis.

The vancomycin AUC_{24h} threshold of 600 mg*h/L for nephrotoxicity was primarily extrapolated from studies that assessed the general population.[4,8-12] They demonstrated that AUC_{24h} values greater than thresholds ranging from 550 to 800 mg*h/L were significantly associated with an increased likelihood of nephrotoxicity.[1-6] It is unclear if this upper threshold is consistent or varies when used in special populations such as critically ill patients, obese patients, patients with preexisting renal disease, and patients on concomitant nephrotoxins.[4] ICU patients and obese patients were shown to be associated with a significantly higher risk of vancomycin-associated nephrotoxicity.[9,13-16] Preexisting renal disease and concomitant nephrotoxins were also shown to play a synergistic role with vancomycin in increasing the risk

of vancomycin-associated nephrotoxicity.[17-20] However, literature assessing the vancomycin AUC_{24h} threshold for nephrotoxicity in the aforementioned special populations is limited and warrants further investigation.

Definition of Terms

Definitions of the terms commonly used in this study are defined in **Table 1**.

Table 1
Key Terms and Definitions

Term	Definition
AUC_{24h}	The area under the concentration-time curve over 24 hours which represents the cumulative drug exposure over 24 hours.
MIC	The lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro.
AUC_{24h}/MIC	The 24-hour area under the concentration-time curve over MIC ratio.
Peak Concentration	The highest serum concentration reached by a drug following an administered dose.
Trough Concentration	The lowest serum concentration reached by a drug before the next dose is administered.
Steady State	The state when the rate of drug intake equals its rate of elimination.
Bayesian PK	The prediction of PK parameters and dosing regimens by integrating information gathered from population PK and the patient's measured drug levels.
CART Analysis	The use of classification to create a predictive model that predicts the value of an outcome or dependent variable using known values of explanatory variables.
CART-Derived Threshold	Used in this study to refer to the vancomycin AUC_{24h} threshold for nephrotoxicity that was derived from this study's CART analysis.
Guideline Threshold	Used in this study to refer to the vancomycin AUC_{24h} threshold of 600 mg*h/L for nephrotoxicity recommended by the 2020 ASHP/IDSA/PIDS/SIDP updated vancomycin monitoring guideline.
PPV	The probability of patients with a positive screening test truly having the condition.
NPV	The probability of patients with a negative screening test truly not having the condition.
Sensitivity	The proportion of patients with a condition who are correctly identified by a screening test as truly having that condition.
Specificity	The proportion of patients without a condition who are correctly identified by a screening test as truly not having that condition.
Area under the ROC Curve	A combined measure of sensitivity and specificity which numerically provides the overall predictive performance of a screening test or diagnostic test.

Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; MIC, minimum inhibitory concentration; AUC_{24h}/MIC, 24-hour area under the concentration-time curve over the minimum inhibitory concentration ratio; PK, pharmacokinetics; CART, classification and regression tree; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

Purpose and Objectives

The purpose of this study is to investigate the generalizability of the proposed vancomycin AUC_{24h} threshold of 600 mg*h/L for nephrotoxicity. The primary objective is to determine the optimal Bayesian-derived AUC_{24h} threshold to minimize vancomycin-associated nephrotoxicity in special populations such as intensive care unit (ICU) or critically ill patients and obese patients. In addition, this study investigated the optimal Bayesian-derived AUC_{24h} threshold for nephrotoxicity in patients with preexisting renal disease and patients on concomitant nephrotoxins other than vancomycin.

Research Questions

1. For each special population, what is the CART-derived AUC_{24h} threshold for vancomycin-associated nephrotoxicity?
    a. ICU or Critically Ill Patients
    b. Obese Patients
    c. Patients with Preexisting Renal Disease
    d. Patients on Concomitant Nephrotoxins
        i. Loop diuretics
        ii. Angiotensin-Converting Enzyme Inhibitors (ACEIs) or Angiotensin II Receptor Blockers (ARBs)
        iii. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
        iv. Aminoglycosides
        v. Piperacillin-Tazobactam
        vi. Intravenous (IV) Contrast Dyes
2. For each special population, how do the predictive performances (i.e., positive predictive value [PPV], negative predictive value [NPV], sensitivity, specificity, and area under the ROC curve) of the CART-derived AUC_{24h} threshold and guideline threshold compare to one another?

a. ICU or Critically Ill Patients

b. Obese Patients

c. Patients with Preexisting Renal Disease

d. Patients on Concomitant Nephrotoxins

    i. Loop diuretics

    ii. ACEIs or ARBs

    iii. NSAIDs

    iv. Aminoglycosides

    v. Piperacillin-Tazobactam

    vi. IV Contrast Dyes

CHAPTER 2: REVIEW OF THE LITERATURE

Methods to Estimate Vancomycin AUC_{24h}

In a retrospective observational study, vancomycin's efficacy and safety were shown to be more closely related to AUC_{24h} and AUC_{24h}/MIC ratio versus trough concentrations.[21] Given vancomycin's narrow range to optimize efficacy and minimize nephrotoxicity, an accurate method of calculating the AUC_{24h} is needed.[4] Until recently, the traditional method of using multiple PK samples and the linear-trapezoidal formula was used to calculate AUC_{24h}. However, the practical difficulties of this method for vancomycin monitoring are why trough concentrations were originally used as surrogate markers for AUC_{24h}.[4] Pai et al. proposed two simplified approaches that were shown to have a high precision and low bias despite only using one to two vancomycin concentrations.[3]

The first approach relies on Bayesian software programs, population modeling, and one or more vancomycin concentrations to estimate the AUC_{24h}.[3] By using a Bayesian approach, probabilities defined as the Bayesian priori and Bayesian posteriori are predicted.[22] The Bayesian priori uses a population PK model and identifies demographic, pathophysiological, environmental, and drug-related factors that can impact vancomycin's disposition. Vancomycin's PK parameters and AUC_{24h} are estimated for each patient by predicting how vancomycin will behave based on prior knowledge about the parameters of interest from previous patient population data. Contrastingly, the Bayesian posteriori involves using patient-specific information such as trough concentrations and peak concentrations to revise or update the estimations of the PK parameters of interest and AUC_{24h}.[22] The Bayesian method is shown to be as accurate as the traditional first-order PK method of using the linear-log trapezoidal

rule.[23] Using a dataset derived from 19 ICU patients, Turner et al. compared the AUC values estimated by multiple Bayesian dose-optimizing software programs to the AUC values calculated using the linear-log trapezoidal rule (AUC_{REF}). The study obtained vancomycin serum levels during the vancomycin infusion, at the end of the infusion, at 60, 120 and 300 minutes after the infusion, and immediately before the next dose of vancomycin. In the study, accuracy was defined as the median ratio of the estimated AUC to AUC_{REF} and bias was defined as the median of the absolute value of the percentage difference between the estimated AUC from AUC_{REF} [(|AUC – AUC_{REF}|/AUC_{REF}) x 100]. With one to two vancomycin concentrations, the Bayesian method produced average accuracy ratios of 0.80 or higher and a bias of less than 20% which are expected to be adequate when targeting an AUC_{24h} of 400 to 600 mg*h/L.[23]

The second approach proposed by Pai et al. uses first-order PK equations and two steady state vancomycin concentrations that are obtained during the same dosing interval.[3] With this method, a trough concentration and peak concentration are obtained to create a simple mono-exponential curve. The snapshot of the patient's vancomycin dosing regimen is then used, along with first-order PK equations, to calculate the AUC_{24h}. With a dataset of 47 intensively sampled adults who received vancomycin, Pai et al. used a Bayesian-derived AUC_{24h} from all vancomycin samples inputted as a reference to assess the accuracy of the second approach which only used two vancomycin samples. Their results showed that the simplified equation-based approach tends to underpredict or overpredict the AUC_{24h} by 2% or less which they deemed as clinically insignificant.[9]

Despite having a similar accuracy as the Bayesian method, the second approach has a major downfall of only being able to provide a static estimation of the AUC_{24h} during the specific time period when the concentration levels were collected.[23] Therefore, the second

approach must be used at steady state and does not account for continuing acute physiologic changes such as renal impairment that can occur during or after the collecting period. Slight lab errors during the collecting period of the two samples can also make a considerable impact on the estimation of the PK values. For example, a vancomycin concentration that is collected too early may still be in the alpha phase and lead to erroneous estimates of the rate of elimination for the simple mono-exponential curve. Contrastingly, the Bayesian method can use vancomycin concentrations obtained at any time. It can estimate the AUC_{24h} at steady state despite the sample being drawn before steady state. This is especially advantageous for patients who are limited on being able to achieve steady state such as critically ill patients. Another downfall to using first-order PK equations is that it creates a simple mono-exponential curve rather than capturing vancomycin's two-compartment distribution and elimination.[23] On the other hand, the Bayesian method allows for application of multiple PK models including a two-compartment model. It can also be modified to be an adaptive program that can account for different dosing patterns such as when loading doses are given or when covariates such as creatinine clearance are unstable.[3]

Therefore, this study followed the first approach proposed by Pai et al. to estimate the AUC_{24h} values.[3] The Bayesian software program used in this study was PrecisePK (Version 20.02.00, Healthware Inc., San Diego, CA) and one or more trough concentrations were used to calculate the Bayesian posteriori.

AUC_{24h}/MIC Threshold for Vancomycin's Efficacy

The broth microdilution (BMD) method and Etest are the two most common methods to estimate the minimum inhibitory concentration (MIC) of staphylococci. The Etest generally predicts the MIC to be 1.5- to 2-fold higher than the MIC calculated using the BMD method after

log conversion.[24] An AUC_{24h}/MIC_{BMD} ratio of 400 to 600 approximately corresponds to an AUC_{24h}/MIC_{Etest} ratio of 200 to 400. For vancomycin dosing in nonserious infections, the variability between the methods to estimate the MIC can be insignificant. However, the standardization and confirmation of the MIC method is imperative for patients with serious MRSA infections who require prompt achievement of the target AUC_{24h}/MIC ratio. Therefore, the 2020 ASHP/IDSA/PIDS/SIDP updated vancomycin monitoring guideline recommends using the BMD method to estimate the MIC as most AUC_{24h}/MIC ratio data were generated using MIC_{BMD}.[4] Currently, an AUC_{24h}/MIC_{BMD} ratio greater than or equal to 400 is recommended as the optimal PK target for vancomycin's efficacy for serious MRSA infections.

The AUC_{24h}/MIC_{BMD} ratio of greater than or equal to 400 is supported by in vitro and in vivo research on the PK and PD of vancomycin.[4,25] Animal model studies demonstrated a 1- to 2-log reduction in bacterial inoculum when the vancomycin AUC_{24h}/MIC_{BMD} ratio is greater than 400.[4] Additionally, in vitro data on two strains of methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA showed that an AUC_{24h}/MIC_{BMD} ratio less than 400 increases vancomycin resistance and the development of vancomycin-intermediate *Staphylococcus aureus* strains. The vancomycin MIC of both strains increased from 1 mg/L to 4 mg/L within 144 hours of subtherapeutic vancomycin exposure.[25]

Initially, studies on the relationship between AUC/MIC ratio and the clinical efficacy of vancomycin were small-scale retrospective studies that used a formula-based approach to estimate the AUC values.[2,4,12,26-28] Moise et al. retrospectively evaluated patients with hospital-acquired pneumonia due to MSSA or MRSA.[28] Based on 70 patients, Moise-Broder et al. determined that there was a significantly higher clinical success rate in patients with AUC_{24h}/MIC_{BMD} ratios greater than or equal to 350 (odds ratio [OR], 7.19; 95% CI, 1.91-27.3;

p=0.0036). Additionally, the median duration for bacteriological eradication of MSSA and MRSA was significantly shorter for patients with AUC_{24h}/MIC_{BMD} ratios greater than or equal to 350 (10 days vs. excess of 30 days; p=0.0402).[28] Similar methods were done on studies evaluating patients with MRSA bacteremia.[2,26,27] Kullar et al. conducted a retrospective cohort study of 320 adults with MRSA bacteremia and identified an AUC_{24h}/MIC_{BMD} threshold of 421 using a classification and regression tree (CART) analysis.[2] Patients with AUC_{24h}/MIC_{BMD} ratios less than 421 had a significantly higher rate of treatment failure (61.2% vs. 48.6%; p=0.038). Likewise, Holmes et al. and Jung et al. assessed patients with MRSA bacteremia and reported similar AUC_{24h}/MIC_{BMD} thresholds.[26,27] Holmes et al. followed a multicenter observational cohort of 182 adults. Patients who achieved an AUC_{24h}/MIC_{BMD} ratio greater than 373 had a significantly lower rate of 30-day mortality (71.6% vs. 84.3%; p=0.043).[27] Jung et al. assessed 76 patients with MRSA bacteremia and determined that an AUC_{24h}/MIC_{BMD} ratio less than 398.5 was associated with a higher rate of treatment failure (45.0% vs. 23.2%; p=0.065).[26] In a retrospective cohort study of 44 patients with MRSA bacteremia, Mogle et al. used the trapezoidal rule and two-point PK approach to estimate AUC_{24h}.[12] Patients with AUC_{24h}/MIC_{BMD} ratios greater than or equal to 297 had a greater than 2.7-fold increase in clinical success (94.4% vs. 50.0%; p=0.01).

Instead of using the formula-based approach, recent studies used the Bayesian method to estimate the AUC values.[21,29] In a retrospective study of 123 cases of MRSA bacteremia, Lodise et al. determined that treatment failure significantly decreased when day 1 $AUC_{0\text{-}24h}/MIC_{BMD}$ ratios were greater than 521 (relative risk [RR], 0.54; 95% CI, 0.32-0.91; p=0.02). Patients with $AUC_{24\text{-}48h}/MIC_{BMD}$ ratios greater than 650 on day 2 also had a significant reduction in treatment failure (RR, 0.58; 95% CI, 0.34-0.99; p=0.05).[21] Casapao et al. evaluated 139 patients with

definite or possible MRSA infective endocarditis. Even after adjusting for factors such as presence of heterogenous vancomycin-intermediate *Staphylococcus aureus,* ICU admission, IV drug use, previous hospitalization, and age, they determined that treatment failure remained significantly higher for patients with $AUC_{0\text{-}24h}/MIC_{BMD}$ ratios less than or equal to 600 (aOR, 2.331; 95% CI, 1.012-5.371; p=0.047).[29]

Two studies used a similar Bayesian approach to estimate AUC_{24h} but only used MIC_{Etest} to calculate the AUC_{24h}/MIC ratio.[30,31] Brown et al. included 18 patients with infected endocarditis and 32 patients with complicated bacteremia (e.g., patients with two positive blood cultures and metastatic foci of the infection).[30] They determined that patients who had AUC_{24h}/MIC_{Etest} ratios less than 211 had a greater than 4-fold increase in death (38% vs. 8%; p=0.02). On the other hand, Garwonoski et al. evaluated 59 patients who had MRSA bacteremia and osteomyelitis.[31] Patients with AUC_{24h}/MIC_{Etest} ratios greater than 293 were associated with a 2.5-fold decrease in time to microbiological clearance (4 ± 2 days vs. 6 ± 3 days; p=0.01). Due to the MIC_{Etest} usually being 1.5- to 2-fold higher than the MIC_{BMD}, the AUC_{24h}/MIC_{Etest} thresholds are suspected to align with the AUC_{24h}/MIC_{BMD} thresholds determined by previous studies.[21,29-31]

The extrapolation of using an AUC/MIC_{BMD} ratio of 400 to 600 is limited because it is primarily based on retrospective, single-center analyses. Therefore, Lodise et al. conducted a prospective, multicenter study that assessed the relationship between AUC/MIC ratios on day 2 and clinical outcomes in 265 adult patients with MRSA bacteremia.[32] No AUC/MIC_{BMD} threshold for vancomycin's clinical efficacy was identified due to only 20% of the study population having AUC/MIC_{BMD} ratios less than 400 mg*h/L. They recommended to continue

maintaining an AUC/MIC_{BMD} ratios greater than 400 mg*h/L as it remains unclear if vancomycin's clinical efficacy is maintained below that threshold.

The vancomycin AUC_{24h}/MIC_{BMD} target is primarily derived from patients with *Staphylococcus aureus* bacteremia, pneumonia, osteomyelitis, and endocarditis.[4] Hence, research on the AUC_{24h}/MIC_{BMD} threshold in other MRSA-associated infections such as skin and soft tissue infections (SSTI), necrotizing fasciitis, infected hardware, and septic joints and in vancomycin special populations such as amphetamine users, IV drug users (IVDU), critically ill patients, and patients on concomitant immunosuppressants is warranted. The current study initially included the objective of assessing the aforementioned MRSA-associated infections and vancomycin special populations and their AUC_{24h}/MIC_{BMD} thresholds for clinical efficacy. However, the study was unable to accomplish this objective due to limitations explained in Chapter 5.

AUC_{24h} Threshold for Vancomycin-Associated Nephrotoxicity

An AUC_{24h} of 600 mg*h/L is currently recommended as the upper threshold for vancomycin to minimize the risk of nephrotoxicity.[4] The threshold was based on collective literature that showed the risk of vancomycin-associated nephrotoxicity increases along the AUC continuum and is at its highest when AUC_{24h} is greater than 550 to 800 mg*h/L.

In a retrospective study of 31 patients, Suzuki et al. compared the highest Bayesian-derived AUC_{24h} values during the treatment period versus the occurrence of nephrotoxicity.[8] A majority of the patients who did not develop nephrotoxicity had AUC_{24h} values between 400 to 600 mg*h/L while most patients who experienced nephrotoxicity had AUC_{24h} values between 600 to 800 mg*h/L (p=0.014). Allen et al. conducted a retrospective cohort study of 278 patients.[32] They compared the incidence of nephrotoxicity between patients with $AUC_{0\text{-}24h}$

values less than 700 mg*h/L and patients with $AUC_{0\text{-}24h}$ values greater than 700 mg*h/L.[33] Patients above the prespecified threshold had a significantly higher incidence of nephrotoxicity (24.5% vs. 13.1%; p=0.021).

Moreover, studies identified CART-derived vancomycin AUC thresholds for nephrotoxicity and suggested that the risk of nephrotoxicity increases in relation to AUC_{24h}.[33-36] Lodise et al. assessed 166 patients and calculated $AUC_{0\text{-}24h}$ using a Bayesian method.[33] They observed that an $AUC_{0\text{-}24h}$ greater than or equal to 1,300 mg*h/L increased the risk of vancomycin-associated nephrotoxicity (25.9% vs. 10.1%; p=0.05). Zasowski reported similar findings in a multicenter, retrospective study of 323 patients.[34] The incidence of nephrotoxicity significantly increased when $AUC_{0\text{-}24h}$ was greater than or equal to 677 mg*h/L, $AUC_{24\text{-}48h}$ was greater than or equal to 683 mg*h/L, and $AUC_{0\text{-}48h}$ was greater than or equal to 1218 mg*h/L. In a retrospective study of 127 patients, Chavada et al. also demonstrated a similar relationship between $AUC_{0\text{-}24h}$ and vancomycin-associated nephrotoxicity.[35] Patients with $AUC_{0\text{-}24h}$ values greater than the CART-derived threshold of 565 mg*h/L had a significantly greater risk of nephrotoxicity (40% vs. 11.2%; p=0.002). Furthermore, Chavada et al. observed that the risk of nephrotoxicity increased by 0.2% as $AUC_{0\text{-}24h}$ increased by 1 mg*hr/L (OR, 1.002; 95% CI, 1.001-1.004; p=0.021). Lastly, Lodise et al. conducted a multicenter, prospective observational study of 265 adults with MRSA bacteremia and determined that the risk of AKI continually increased as $AUC_{24\text{-}48h}$ increased. In their study, patients with $AUC_{24\text{-}48h}$ values greater than or equal to 793 mg*h/L had the highest risk of AKI (RR, 0.16; 95% CI, 0.04-0.29).[36]

Aljefri et al. conducted a meta-analysis on randomized case-control and cohort studies that reported AUC values and the incidence of nephrotoxicity.[10] Including the aforementioned studies, the meta-analysis consisted of six retrospective studies and two prospective studies. The

studies estimated AUC using a Bayesian approach with the exception of the study by Finch et al. Because the studies reported multiple AUC values (e.g., $AUC_{0\text{-}24h}$ and $AUC_{24\text{-}48h}$) that ranged from 550 to 700 mg*h/L, an endpoint of 650 mg*h/L was used to define low versus high AUC values. Patients with low $AUC_{0\text{-}24h}$ values had a significantly lower risk of AKI than those with high $AUC_{0\text{-}24h}$ values (OR, 0.36; 95% CI, 0.23-0.56; $p<0.001$). Patients with low $AUC_{24\text{-}48h}$ values also had similar results (OR, 0.68; 95% CI, 0.46-0.99; $p=0.002$).[4] Similarly, Mogle et al. identified a CART-derived AUC_{24h} threshold of 710 mg*h/L.[12] Patients with AUC_{24h} values greater than or equal to 710 mg*h/L within the first 96 hours of vancomycin had a higher rate of nephrotoxicity (33.3% vs. 2.5%; $p=0.04$).

The aforementioned studies defined vancomycin-associated nephrotoxicity as an increase in serum creatinine (SCr) by greater than or equal to 0.5 mg/dL or a 50% increase from baseline on two or more consecutive measures.[8,12,32-36] However, this study defined vancomycin-associated nephrotoxicity as an increase in SCr by 0.3 mg/dL or more within 48 hours while on vancomycin or an increase in SCr by 1.5 times the baseline which is known or presumed to have occurred within seven days of discontinuing vancomycin.[37] A less stringent definition of vancomycin-associated nephrotoxicity was used to include more nephrotoxic patients. Additionally, studies did not examine the vancomycin AUC_{24h} thresholds for nephrotoxicity in vancomycin special populations.[8,12,32-36] Rather, they assessed the thresholds for the general population of patients who were on vancomycin. More studies are needed to determine if the vancomycin AUC_{24h} threshold for nephrotoxicity is altered in certain vancomycin special populations. This is especially important for vancomycin special populations that are associated with an increased risk of vancomycin-associated nephrotoxicity such as the ones discussed in the next section.

Vancomycin PK and PD Changes in Special Populations

Studies on the use of vancomycin in special populations such as critically ill patients, obese patients, patients with preexisting renal disease, and patients on concomitant nephrotoxins showed that the PK and PD of vancomycin can be altered as a result of physiological changes.[13,17,18,20,24,38-40] Thus, these special populations can have an increased risk of adverse effects from vancomycin. Host-related factors such as critical illness, increased weight, preexisting renal disease, and concomitant nephrotoxic agents have been associated with an increased risk of vancomycin-associated nephrotoxicity.[14-16,33,41-43] However, there are currently no studies that investigate whether the AUC_{24h} threshold for vancomycin-associated nephrotoxicity changes when used in the aforementioned special populations.[4] Therefore, analyses on their vancomycin AUC_{24h} thresholds for nephrotoxicity are warranted.

Critically Ill or ICU Patients

Critically ill patients require larger doses of vancomycin due to their high acuity and their offending pathogens being less susceptible.[13] They also tend to have hemodynamic instability and renal hypoperfusion that can increase their risk of nephrotoxicity. Furthermore, vancomycin's altered volume of distribution (V_d) in critically ill patients increases the risk of nephrotoxicity.[13,38] Critically ill patients with severe sepsis can experience fluid shifts from the intravascular compartment to the interstitial space due to excessive fluid resuscitation, widespread endothelial injury, and capillary leakages.[13] This results in altering the PK of hydrophilic drugs like vancomycin by causing an increase in V_d and a decrease in plasma concentration.[13,38]

Studies demonstrated that variables independently associated with vancomycin-associated nephrotoxicity are ICU residence (aOR, 3.25; 95% CI, 1.18-9.98; p=0.02) and a high

Acute Physiology and Chronic Health Evaluation (APACHE) II score (22.9 ± 7.4 vs. 18.2 ± 8.5; p=0.006).[16,33] In a retrospective study of 166 patients, Lodise et al. also showed that ICU patients have a greater than 20% probability of experiencing nephrotoxicity with initial trough concentrations greater than 10 mg/L.[33]

Obese Patients

Physiologic changes in obese patients have been shown to alter the V_d of vancomycin.[39] Obese patients have a higher V_d of vancomycin due to having higher levels of lean body mass and larger organs than patients of normal weight.[40,44] Despite vancomycin being hydrophilic, high levels of adipose tissue are also suspected to play a role in increasing the V_d. Due to water accounting for approximately 30% of the content of adipose tissues, vancomycin is able to distribute in the adipose tissue to a certain extent.[39,40] Additionally, obese patients experience increased blood flow due to having a higher blood volume and cardiac output.[40] In combination with vancomycin's hydrophilic nature, their increased blood flow can contribute to a higher V_d.

Currently, there are conflicting studies on the relationship between obesity and the risk of vancomycin-associated nephrotoxicity. [14,15,42,43,45] In a retrospective study of 207 obese patients with a body mass index (BMI) greater than 30 kg/m^2 and 323 lean patients, obesity was not associated with an increased risk of nephrotoxicity (RR, 0.98; 95% CI, 0.93-1.04; p=0.59).[45] Contrastingly, there are multiple studies that suggest a relationship between obesity and an increased risk of vancomycin-associated nephrotoxicity.[14,15,42,43] In a multicenter, retrospective study of 337 patients, weight greater than 100 kg was found to be an independent predictor of nephrotoxicity (OR, 2.74; 95% CI, 1.27-5.91).[14] In a retrospective study of 270 veterans, Horey et al. also found weight to be significantly associated with an increased risk of nephrotoxicity (OR, 1.02; 95% CI, 1.00-1.03).[15] Furthermore, Choi et al. demonstrated that obesity class III

(BMI ≥40 kg/m^2) patients have a 3-fold greater risk of vancomycin-associated nephrotoxicity compared to obesity class I and II (BMI 30-39.9 kg/m^2) patients and nonobese patients (OR, 3.14; 95% CI, 1.27-7.75 and OR, 2.99; 95% CI, 1.12-7.94, respectively).[42] These findings are consistent with results from a retrospective cohort study of 246 patients conducted by Lodise et al. which showed that patients who weigh greater than or equal to 101.4 kg were approximately 3.5 times more likely to develop nephrotoxicity (HR, 3.65; 95% CI 2.52-5.28, p<0.001).[43] A mechanistic explanation for obesity being associated with an increased risk of vancomycin-associated nephrotoxicity remains unclear. However, studies hypothesize that a likely factor is the large V_d that causes disproportionately larger doses of vancomycin and a more intensive vancomycin exposure profile.[42,43]

Patients with Preexisting Renal Disease

Patients with preexisting renal disease are at a higher risk of developing vancomycin-associated nephrotoxicity.[20] Vancomycin is primarily eliminated renally and its extrarenal clearance is approximately 5%.[17] Vancomycin is predominantly cleared through glomerular filtration and through active tubular secretion to a certain degree. With a decrease in renal function, the half-life of vancomycin increases linearly. Thus, patients with preexisting renal disease have a higher risk of vancomycin accumulating. Normally, the half-life of vancomycin is six hours. However, in patients with anuria, the half-life can soar up to 100 to 200 hours. As vancomycin accumulates, there is a higher risk of vancomycin overdosing and subsequent nephrotoxicity.

Patients on Concomitant Nephrotoxins

Vancomycin has been shown to decrease the threshold for nephrotoxicity and has demonstrated synergistic activity with other nephrotoxins administered concomitantly.[18,20]

Studies demonstrated that the coadministration of nephrotoxins such as loop diuretics, renin-angiotensin system blockers, NSAIDs, aminoglycosides, piperacillin-tazobactam, and IV contrast dyes increases the risk of renal toxicity.[18,46-50] In a prospective cohort study of 95 patients, Hidayat et al. determined that patients on concomitant nephrotoxins were significantly associated with an increased risk of nephrotoxicity (91% vs. 20%; $p<0.001$).[19] Even after performing a multivariate analysis and controlling other significant factors such as age, APACHE II score, admission to ICU, vancomycin trough concentrations, and duration of vancomycin therapy, coadministration of nephrotoxins remained the most significant predictor of nephrotoxicity occurrence ($p=0.003$).

Matson et al. demonstrated that the concomitant use of loop diuretics, ACEIs, and NSAIDs increases the risk of vancomycin-associated nephrotoxicity by 43-fold, 5-fold, and 19-fold, respectively.[18] For aminoglycosides, Rybak et al. assessed 224 patients who received vancomycin alone, gentamicin alone, or vancomycin plus an aminoglycoside.[47] Patients who received both vancomycin and an aminoglycoside had a significantly higher rate of nephrotoxicity than patients who received vancomycin or gentamicin alone (22% vs. 5% vs. 11%, respectively; $p<0.05$). Similarly, Hanrahan et al. assessed 158 critically ill patients and demonstrated that concomitant aminoglycosides with vancomycin increased the occurrence of nephrotoxicity (OR, 18.9; $p=0.002$).[48]

Although piperacillin-tazobactam is not considered a nephrotoxin, piperacillin-tazobactam has been associated with impaired renal recovery and acute interstitial nephritis.[24] Meta-analyses have also suggested that vancomycin with piperacillin-tazobactam can increase the risk of nephrotoxicity.[49,50] Hammond et al. conducted a meta-analysis and analyzed 14 studies.[49] They concluded an adjusted OR of 3.11 (95% CI, 1.77-5.47; $p<0.001$) for

nephrotoxicity was significant when vancomycin plus piperacillin-tazobactam was compared to vancomycin plus a beta-lactam antibiotic. Similarly, Giuliano et al. evaluated 15 studies and calculated an overall OR of 3.65 (95% CI, 2.16-6.17; $p<0.001$) which was significant when vancomycin in combination with piperacillin-tazobactam was compared to vancomycin alone.[50]

CHAPTER 3: METHODOLOGY

Study Design and Population

The study design is a single-institution retrospective cohort study at San Joaquin General Hospital (SJGH), a 196-bed county hospital located in Stockton, California. The study was approved by the University of the Pacific (UOP) Institutional Review Board (IRB) with protocol number 20-122 and by the SJGH IRB with protocol number 20-303. Medical records were reviewed at SJGH to identify hospitalized patients treated with IV vancomycin between June 2019 to May 2020. Patient identifiable information was removed upon completing the data collection. Inclusion criteria were patients who were 18 years or older, required vancomycin for the treatment of an infection, on vancomycin for 48 hours or longer, and had one or more vancomycin concentrations collected. Exclusion criteria were pregnancy, vancomycin continued for an infection diagnosed from a previous admission, any form of renal replacement therapy, vancomycin for surgical prophylaxis, and vancomycin continuous infusion.

Data Collection

Baseline demographics. The following baseline demographics were collected.

- Gender
- Age
- Weight
- Height
- Ethnicity
- Comorbidities (e.g., preexisting liver disease, atherosclerotic cardiovascular disease [ASCVD], heart failure, diabetes, hypertension, amphetamine use, and IV drug use)

Clinical characteristics. The following clinical characteristics were collected.

- SCr upon initiating vancomycin
- Number of days on vancomycin
- Suspected or diagnosed infection that indicated the use of vancomycin (e.g., SSTI, necrotizing fasciitis, osteomyelitis, pneumonia, bacteremia, endocarditis, septic joint, empyema)

Isolated bacterial species. Based on microbiological reports, patients were categorized as having MRSA, non-MRSA isolated bacterial species, or no isolated bacterial species.

- MRSA: Isolated pathogen was MRSA.
- Non-MRSA Isolated Bacterial Species: Isolated pathogen was not MRSA but was still covered by vancomycin's spectrum of activity (e.g., *Enterococcus spp.* and MSSA).
- No Isolated Bacterial Species: Isolated pathogen that is not covered by vancomycin's spectrum of activity (e.g., gram-negative bacteria) or no positive cultures obtained during the hospital stay.

Special populations. Medical charts were reviewed to place patients into vancomycin special populations of interest: ICU or critically ill patients and obese patients.

- ICU or Critically Ill Patients: Patients who required an admission to the medical ICU or surgical ICU during their vancomycin course of treatment.
- Obese Patients: Patients with a BMI greater than or equal to 30 kg/m^2 upon initiating vancomycin.

Preexisting renal disease and concomitant nephrotoxins. Medical charts were reviewed to assess for patients with preexisting renal disease and patients on concomitant nephrotoxins other than vancomycin.

- Patients with Preexisting Renal Disease: Patients who have chronic kidney disease or patients admitted with AKI that was unrelated to vancomycin.

- Patients on a Concomitant Nephrotoxin: Patients who received one or more doses of a loop diuretic, ACEI, ARB, NSAID, aminoglycoside, piperacillin-tazobactam, or IV contrast dye while on vancomycin.

Steady state AUC_{24h}. Using the Bayesian software program, PrecisePK (Version 20.02.00, Healthware Inc., San Diego, CA), the patient's age, gender, weight, height, SCr history, vancomycin dosing history, and vancomycin trough concentrations were entered into the program to calculate the AUC_{24h}. By assessing the concentration versus time graph, an interval when vancomycin's steady state was reached and consistent was identified. To decrease variability, the steady state was determined consistent if each of the dose's peak concentrations was ±10% of its respective dosing regimen's total average peak concentration. The AUC_{24h} for the steady state interval was then calculated using the equation below.

- $\mathrm{AUC}_{24\mathrm{h}}\left(in\ \frac{mg*h}{L}\right) = \frac{\mathrm{AUC}_2\left(in\frac{mg*h}{L}\right) - \mathrm{AUC}_1\left(in\frac{mg*h}{L}\right)}{\mathrm{t}_2\ (in\ hours) - \mathrm{t}_1(in\ hours)} * 24\ \mathrm{hours}$

Endpoints. The primary endpoint is vancomycin-associated nephrotoxicity using the definition of nephrotoxicity from the 2012 KDIGO Clinical Practice Guideline for AKI.

- Vancomycin-Associated Nephrotoxicity: An increase in serum creatinine by 0.3 mg/dL or more within 48 hours while on vancomycin or an increase in serum creatinine by 1.5 times the baseline which is known or presumed to have occurred within seven days of discontinuing vancomycin.

The secondary endpoint is the estimated vancomycin AUC_{24h} thresholds for nephrotoxicity for critically ill or ICU patients, obese patients, patients with preexisting renal disease, and patients on concomitant nephrotoxins.

The tertiary endpoint is the predictive performances of the vancomycin AUC_{24h} thresholds which include the following parameters:[51,52]

- Positive Predictive Value (PPV): The probability of patients with a positive screening test truly having the condition. For this study, the PPV is the probability of patients

with AUC_{24h} values greater than the threshold for nephrotoxicity actually experiencing vancomycin-associated nephrotoxicity.

- Negative Predictive Value (NPV): The probability of patients with a negative screening test truly not having the condition. For this study, the NPV is the probability of patients with AUC_{24h} values less than the threshold for nephrotoxicity actually not experiencing vancomycin-associated nephrotoxicity.

- Sensitivity: The proportion of patients with a condition who are correctly identified by a screening test as truly having that condition (i.e., identifying true positives). For this study, the sensitivity is the proportion of nephrotoxic patients who are correctly identified as experiencing vancomycin-associated nephrotoxicity based on the AUC_{24h} threshold for nephrotoxicity.

- Specificity: The proportion of patients without a condition who are correctly identified by a screening test as truly not having that condition (i.e., identifying true negatives). For this study, the specificity is the proportion of non-nephrotoxic patients who are correctly identified as not experiencing vancomycin-associated nephrotoxicity based on the AUC_{24h} threshold for nephrotoxicity.

- Area Under the Receiver Operating Characteristic (ROC) Curve: A combined measure of sensitivity and specificity which numerically provides the overall predictive performance of a screening test or diagnostic test. As the area under the ROC curve increases towards a maximum value of one, the overall performance of the test increases. For this study, it is the overall predictive performance of the AUC_{24h} threshold for nephrotoxicity.

Data Analysis

Baseline demographics and clinical characteristics were reported using descriptive statistics. Additionally, the relationship between the patients' baseline demographics and clinical characteristics and vancomycin-associated nephrotoxicity was analyzed by comparing nephrotoxic patients to non-nephrotoxic patients. The independent t-test was used to detect statistical differences for continuous data while the Chi-square test and Fisher's exact test were used to detect statistical differences for nominal data.

Each special population that included at least ten nephrotoxic patients was further analyzed to derive the AUC_{24h} threshold where the incidence of nephrotoxicity was most

disproportionate. The AUC_{24h} thresholds were estimated using CART analysis. Their predictive performances were assessed by calculating their PPVs, NPVs, sensitivities, and specificities. The equations below were used to calculate the parameters and an example of the method is displayed in **Table 2**.

- $\text{PPV} = \frac{\text{A}}{\text{A+B}} \text{ x } 100$
- $\text{NPV} = \frac{\text{D}}{\text{C+D}} \text{ x } 100$
- $\text{Sensitivity} = \frac{\text{A}}{\text{A+C}} \text{ x } 100$
- $\text{Specificity} = \frac{\text{D}}{\text{B+D}} \text{ x } 100$

Variables: A, true positive; B, false positive; C, false negative; D, true negative

Table 2
Example of Calculating PPV, NPV, Sensitivity, and Specificity for AUC_{24h} Thresholds Predicting Nephrotoxicity

AUC_{24h} Threshold of 616 mg*h/L		**Nephrotoxic**	**Non-Nephrotoxic**
AUC_{24h} above threshold	Number of Patients	18 ***True Positive (A)***	47 ***False Positive (B)***
	% Within Threshold	27.7% ***PPV***	72.3%
	% Within Nephrotoxicity	62.1% ***Sensitivity***	15.3%
AUC_{24h} less than threshold	Number of Patients	11 ***False Negative (C)***	260 ***True Negative (D)***
	% Within Threshold	4.1%	95.9% ***NPV***
	% Within Nephrotoxicity	37.9%	84.7% ***Specificity***

*Abbreviation*s. PPV, positive predictive value; NPV, negative predictive value; AUC_{24h}, area under the concentration-time curve over 24 hours.

Each CART-derived threshold's predictive performance for predicting nephrotoxicity was then compared to the predictive performance of the AUC_{24h} threshold of 600 mg*h/L that is

currently recommended by the 2020 ASHP/IDSA/PIDS/SIDP updated vancomycin monitoring guideline. A generalized score statistic was used to detect statistical differences between the two thresholds' PPVs and NPVs and the McNemar test was used to detect statistical differences between their sensitivities and specificities. When comparing the predictive performances between the CART-derived thresholds and the guideline threshold, maximizing the PPV and sensitivity is desired over maximizing the NPV or specificity. A higher PPV increases the likelihood of identifying AUC_{24h} values that result in nephrotoxicity. Moreover, a higher sensitivity increases the accuracy of the threshold in predicting patients who truly have nephrotoxicity and decreases the probability of having a false negative. In addition to comparing their predictive values, sensitivities, and specificities, ROC curves were analyzed to compare the thresholds' overall predictive performances.

Prior to identifying and assessing the AUC_{24h} threshold for each special population, a validity test was performed to assess the method proposed by this study. This was achieved by applying the method to the general population. The method was considered validated if the CART-derived threshold for the general population was determined to be insignificant when compared to the guideline threshold that was based on preexisting literature.

Lastly, to evaluate for any confounding factors, patients were divided into two groups: patients who had an AUC_{24h} less than or equal to the CART-derived threshold and those who had an AUC_{24h} above the CART-derived threshold. Bivariate comparisons between the two groups' baseline demographics, clinical characteristics, and types of infection were then conducted. The independent t-test was used to detect statistical differences for continuous data and the Chi-square test and Fisher's exact test were used to detect statistical differences for nominal data.

In this study, *p*-values of less than or equal to 0.05 were considered statistically significant. Statistical analyses such as the independent t-test, Chi-Square test, Fisher's exact test, and CART analysis were performed using IBM SPSS software (Version 27.0, IBM Corporation, Armonk, NY). The generalized score statistic and McNemar test were performed using RStudio software (Version 1.3.1073, RStudio Team, Boston, MA).

CHAPTER 4: RESULTS

Description of Cohort

A total of 336 patients was included in the study. Baseline demographics of the study population are presented in **Table 3**. A majority of the patients were male (84.8%) and Caucasian (41.4%). Among the study population, mean age was 57.1 years (standard deviation [SD], 14.9 years), mean weight was 86.9 kilograms (SD, 28.1 kilograms), and mean height was 173.0 centimeters (SD, 11.4 centimeters). Common comorbidities included ASCVD (21.7%), diabetes (33.9%), hypertension (44.9%), and amphetamine use (20.5%).

Table 3
Baseline Demographics

Characteristic	Value for Patients (*n*=336)
Gender, no. (%)	
Male	285 (84.8)
Female	51 (15.2)
Age (years), mean ± SD	57.1 ± 14.8
Weight (kg), mean ± SD	86.9 ± 28.1
Height (cm), mean ± SD	173.0 ± 11.4
Ethnicity/Race, no. (%)	
Caucasian	139 (41.4)
Hispanic	96 (28.6)
Black or African-American	66 (19.6)
Asian	17 (5.1)
Mixed	11 (3.3)
Other	7 (2.1)
Comorbidity, no. (%)	
Preexisting Liver Disease	62 (18.5)
Atherosclerotic Cardiovascular Disease (ASCVD)	73 (21.7)
Heart Failure	40 (11.9)
Diabetes	114 (33.9)
Hypertension	151 (44.9)
Amphetamine Use	69 (20.5)
Intravenous Drug Use	35 (10.4)

Clinical characteristics of the study population are illustrated in **Table 4**. The mean SCr upon initiating vancomycin was 1.06 mg/dL (SD, 0.69 mg/dL) and the mean duration of therapy was 7.2 days (SD, 4.6 days). The most common vancomycin indications were SSTI (34.2%), pneumonia (32.7%), and bacteremia (24.1%), and approximately a quarter of the population's isolated pathogens were MRSA (24.1%).

Table 4
Clinical Characteristics

Characteristic	Value for Patients (*n*=336)
Vancomycin Indication, no. (%)	
SSTI	115 (34.2)
Necrotizing Fasciitis	9 (2.7)
Osteomyelitis	33 (9.8)
Pneumonia	110 (32.7)
Bacteremia	81 (24.1)
Endocarditis	5 (1.5)
Septic Joint	6 (1.8)
Empyema	6 (1.8)
Other	43 (12.8)
Isolated Organism, no. (%)	
MRSA	81 (24.1)
Non-MRSA	103 (30.7)
No organism isolated or vancomycin-resistant organism	152 (45.2)
Initial Serum Creatinine (mg/dL), mean ± SD	1.06 ± 0.69
Vancomycin Duration (days), mean ± SD	7.2 ± 4.6

Abbreviations. SSTI, skin and soft tissue infections; MRSA, methicillin-resistant *Staphylococcus aureus*.

Comparison of Patient Characteristics Between Non-Nephrotoxic and Nephrotoxic Patients

The bivariate comparison of the baseline demographics and clinical characteristics between patients who had nephrotoxicity and those who did not is displayed in **Table 5**. Twenty-nine (8.6%) patients experienced nephrotoxicity. Patients who experienced nephrotoxicity were more likely to have preexisting renal disease (34.5% vs. 14.4%; p=0.014)

and had significantly higher SCr levels upon initiating vancomycin (1.52 ± 0.95 mg/dL vs. 1.02 ±. 0.65 mg/dL; $p<0.001$). Furthermore, the nephrotoxic group had significantly more critically ill or ICU patients (75.9% vs. 30.6%; $p<0.001$) and patients who received concomitant loop diuretics (75.9% vs. 33.9%; $p<0.001$).

Table 5
Patient Characteristics Between Non-Nephrotoxic and Nephrotoxic Patients

Characteristic	Non-Nephrotoxic (*n*=307)	Nephrotoxic (*n*=29)	*P*-value
Demographics			
Age (years), mean ± SD	56.7 ± 14.7	60.5 ± 14.7	0.186[a]
Male, no. (%)	260 (84.7)	25 (86.2)	1.000[b]
Selected Comorbidities			
Preexisting Liver Disease, no. (%)	57 (18.6)	5 (17.2)	0.860
ASCVD, no. (%)	64 (20.8)	9 (31.0)	0.203
Heart Failure, no. (%)	31 (10.1)	9 (31.0)	0.003[b*]
Diabetes, no. (%)	101 (32.9)	13 (44.8)	0.195
Hypertension, no. (%)	130 (42.3)	21 (72.4)	0.002[*]
Selected Special Populations			
Critically Ill or ICU, no. (%)	94 (30.6)	22 (75.9)	<0.001[*]
Obese (BMI≥30 kg/m^2), no. (%)	101 (32.9)	10 (34.5)	0.862
Preexisting Renal Disease, no. (%)	44 (14.4)	10 (34.5)	0.014[b*]
Concomitant Nephrotoxin			
Loop Diuretic, no. (%)	104 (33.9)	22 (75.9)	<0.001[*]
ACEI/ARB, no. (%)	68 (22.2)	6 (20.7)	0.849
NSAID, no. (%)	41 (13.4)	3 (10.3)	1.000[b]
Aminoglycoside, no. (%)	7 (2.3)	2 (6.9)	0.177[b]
Piperacillin/tazobactam, no. (%)	12 (3.9)	0 (0)	0.610[b]
IV Contrast, no. (%)	135 (44.0)	7 (24.1)	0.039[*]
Vancomycin Treatment Data			
Initial SCr (mg/dL), mean ± SD	1.02 ± 0.65	1.52 ± 0.95	<0.001[a*]
Vancomycin Indication			
SSTI, no. (%)	109 (35.5)	6 (20.7)	0.108
Osteomyelitis, no. (%)	31 (10.1)	2 (6.9)	0.753[b]
Pneumonia, no. (%)	95 (30.9)	15 (51.7)	0.023[*]
Bacteremia, no. (%)	77 (25.1)	4 (13.8)	0.174
Vancomycin Duration (days), mean ± SD	7.1 ± 4.6	7.4 ± 4.5	0.775[a]

[*] *P*-value was <0.05.
[a] *P*-value was calculated using independent t-test.
[b] *P*-value was calculated using Fisher's exact test due to one or more expected values being <5. All other *p*-values were calculated using chi-square test.
Abbreviations. ASCVD, atherosclerotic cardiovascular disease; ICU, intensive care unit; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; SSTI, skin and soft tissue infection; SCr, serum creatinine.

Method Validation by Analyzing the General Population

For the general population of 336 patients, the CART analysis showed that the incidence of nephrotoxicity was significantly higher for patients with AUC_{24h} values greater than 616 mg*h/L (27.7% vs. 4.1%; $p<0.001$) (**Figure 1**).

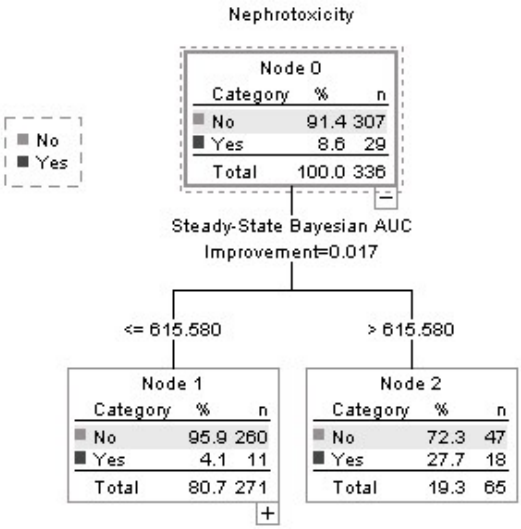

Figure 1. CART-derived AUC_{24h} nephrotoxicity threshold for the general population.

Table 6, **Table 7**, and **Figure 2** compare the predictive performances of the CART-derived threshold and guideline threshold. No statistical differences were detected between their PPVs ($p=0.163$), NPVs ($p=0.286$), and sensitivities ($p=0.157$). Moreover, their overall predictive performances were noninferior to one another as they had similar areas under the ROC curves (0.734 vs. 0.747; $p=0.589$). The threshold of 616 mg*h/L was consistent with previous studies and was associated with practically similar predictive performances to the guideline threshold of 600 mg*h/L.[4]

Table 6

Predictive Performances of CART-Derived AUC_{24h} Threshold and Guideline Threshold for the General Population

Predictive Performance	AUC_{24h} 616 mg*h/L	AUC_{24h} 600 mg*h/L	*P*-value
PPV (%)	27.7	25.0	0.163[a,c]
NPV (%)	95.9	96.5	0.286[a,d]
Sensitivity (%)	62.1	69.0	0.157[b,e]
Specificity (%)	84.7	80.5	<0.001[b,f*]
Area under ROC Curve (95% CI)	0.734 (0.626–0.841)	0.747 (0.646–0.849)	0.589[g]

[*] *P*-value was <0.05

[a] *P*-value was calculated using generalized score statistic.

[b] *P*-value was calculated using McNemar test.

[c] PPV data derived from 145 observations (65 patients with AUC_{24h} >616 mg*h/L and 80 patients with AUC_{24h} >600 mg*h/L).

[d] NPV data derived from 527 observations (271 patients with AUC_{24h} <616 mg*h/L and 256 patients with AUC_{24h} <600 mg*h/L).

[e] Sensitivity data derived from 29 nephrotoxic patients.

[f] Specificity data derived from 307 non-nephrotoxic patients.

[g] ROC analysis derived from 336 patients.

Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

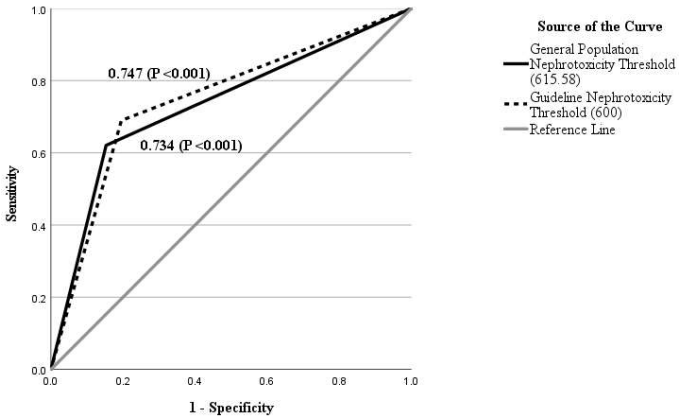

Figure 2. Receiver operating characteristic (ROC) curves of CART-derived AUC_{24h} threshold and guideline AUC_{24h} threshold for the general population.

Table 7
AUC_{24h} of General Population That Experienced Nephrotoxicity

	AUC_{24h} ≤600 mg*h/L	**AUC_{24h} >600 mg*h/L**
AUC_{24h} ≤616 mg*h/L	9 (31.0)	2 (6.9)
AUC_{24h} >616 mg*h/L	0 (0)	18 (62.1)

P-value=0.157 (based on McNemar test); *n*=29
Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours.

Special Populations and Nephrotoxic Patients

Table 8 summarizes the total number of patients and patients with nephrotoxicity in each special population. Special populations of interest included critically ill or ICU patients (34.5%), obese patients (33.0%), patients with preexisting renal disease (16.1%), and patients on concomitant nephrotoxins (76.8%). The most common concomitant nephrotoxins were loop diuretics (37.5%), ACEIs or ARBs (22.0%), and IV contrast dyes (42.3%).

There were at least ten nephrotoxic patients in critically ill or ICU patients, obese patients, patients with preexisting renal disease, and patients on concomitant loop diuretics. The CART-derived AUC_{24h} thresholds were derived for these special populations and their predictive performances were assessed, as described in the method section. Contrastingly, less than ten nephrotoxic patients were observed in patients on concomitant ACEIs or ARBs, NSAIDs, aminoglycosides, piperacillin-tazobactam, or IV contrast dyes. Due to inadequate sample sizes in these special populations, further analyses were not performed.

Table 8
Special Populations and Nephrotoxic Patients

Special Population	Total Patients, no.	Nephrotoxic Patients, no.
Critically Ill or ICU Patient	116	22
Obese Patient (BMI≥30 kg/m^2)	111	10
Patient with Preexisting Renal Disease	54	10
Patient on a Concomitant Nephrotoxin		
Loop Diuretic	126	22
ACEI/ARB	74	6
NSAID	44	3
Aminoglycoside	9	2
Piperacillin/tazobactam	12	0
IV Contrast Dye	142	7

Abbreviations. ICU, intensive care unit; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; IV, intravenous.

CART-Derived Vancomycin AUC_{24h} Thresholds for Nephrotoxicity

Critically Ill or ICU Patients

Of the 336 patients, 116 (34.5%) patients were identified to be critically ill or ICU patients. The CART analysis showed that incidence of nephrotoxicity was significantly higher for critically ill or ICU patients with AUC_{24h} values greater than 544 mg*h/L (35.8% vs. 4.8%; $p<0.001$) (**Figure 3**).

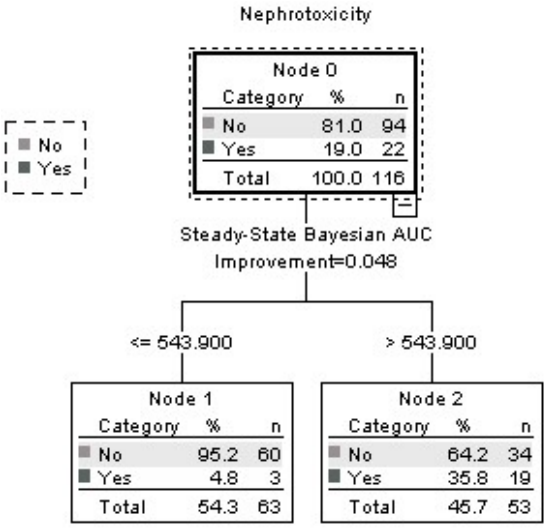

Figure 3. CART-derived AUC_{24h} nephrotoxicity threshold for critically ill and ICU patients.

Table 9 and **Figure 4** display the predictive performances of the CART-derived AUC_{24h} threshold and guideline threshold for critically ill or ICU patients. The CART-derived threshold had a significantly higher NPV (p=0.037) and sensitivity (p=0.031). In other words, out of 22 ICU patients with nephrotoxicity, the threshold of 544 mg*h/L identified six (27.3%) more nephrotoxic patients than the threshold of 600 mg*h/L (**Table 10**). Moreover, the overall predictive performance of the CART-derived threshold was shown to be 0.058 (8.4%) higher than that of the guideline threshold based on the ROC curve analysis (0.751 vs. 0.693; p=0.278). Statistical significance for the ROC analysis was not achieved due to a small sample size.

Table 9

Predictive Performances of CART-Derived AUC_{24h} Threshold and Guideline Threshold for Critically Ill and ICU Patients

Predictive Performance	AUC_{24h} 544 mg*h/L	AUC_{24h} 600 mg*h/L	*P*-value
PPV (%)	35.8	40.6	0.337[a,c]
NPV (%)	95.2	89.3	0.037[a,d*]
Sensitivity (%)	86.4	59.1	0.014[b,e*]
Specificity (%)	63.8	79.8	<0.001[b,f*]
Area under ROC Curve (95% CI)	0.751 (0.646–0.856)	0.694 (0.563–0.825)	0.278[g]

[*] *P*-value was <0.05

[a] *P*-value was calculated using generalized score statistic.

[b] *P*-value was calculated using McNemar test.

[c] PPV data derived from 85 observations (53 patients with AUC_{24h} >544 mg*h/L and 32 patients with AUC_{24h} >600 mg*h/L).

[d] NPV data derived from 147 observations (63 patients with AUC_{24h} <544 mg*h/L and 84 patients with AUC_{24h} <600 mg*h/L).

[e] Sensitivity data derived from 22 nephrotoxic patients.

[f] Specificity data derived from 94 non-nephrotoxic patients.

[g] ROC analysis derived from 116 patients.

Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; ICU, intensive care unit; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

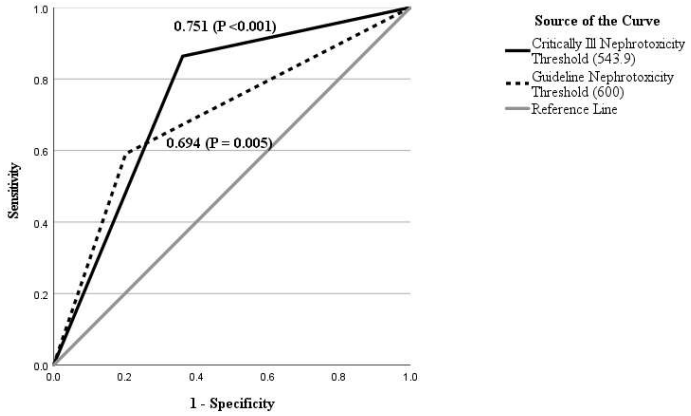

Figure 4. Receiver operating characteristic (ROC) curves of CART-derived AUC_{24h} threshold and guideline AUC_{24h} threshold for critically ill and ICU patients.

Table 10
AUC_{24h} of Critically Ill or ICU Patients Who Experienced Nephrotoxicity

	AUC_{24h} ≤600 mg*h/L	**AUC_{24h} >600 mg*h/L**
AUC_{24h} ≤544 mg*h/L	3 (13.6)	0 (0)
AUC_{24h} >544 mg*h/L	6 (27.3)	13 (59.1)

P-value=0.014 (based on McNemar test); *n*=22
Abbreviations. ICU, intensive care unit; AUC_{24h}, area under the concentration-time curve over 24 hours.

Table 11 provides the bivariate comparison between critically ill or ICU patients with AUC_{24h} values less than or equal to 544 mg*h/L and those with AUC_{24h} values greater than 544 mg*h/L. No confounding factors were found that can impact the risk of vancomycin-associated nephrotoxicity between the two groups.

Table 11

Patient Characteristics Between Critically Ill or ICU Patients with AUC_{24h} Above and Below CART-Derived AUC_{24h} Threshold

Characteristic	AUC_{24h} ≤544 mg*h/L (*n*=63)	AUC_{24h} >544 mg*h/L (*n*=53)	*P*-value
Demographics			
Age (years), mean ± SD	53.7 ± 16.0	60.1 ± 14.7	0.028[a*]
Male, no. (%)	53 (84.1)	41 (77.4)	0.354
Selected Comorbidities			
Preexisting Liver Disease, no. (%)	6 (9.5)	8 (15.1)	0.359
ASCVD, no. (%)	15 (23.8)	10 (18.9)	0.519
Heart Failure, no. (%)	5 (7.9)	12 (22.6)	0.026[*]
Diabetes, no. (%)	19 (30.2)	8 (15.1)	0.056
Hypertension, no. (%)	23 (36.5)	23 (43.4)	0.450
Selected Special Populations			
Obese (BMI≥30 kg/m^2), no. (%)	23 (36.5)	15 (28.3)	0.348
Preexisting Renal Disease, no. (%)	9 (14.3)	14 (26.4)	0.103
Concomitant Nephrotoxin, no. (%)			
Loop Diuretic, no. (%)	34 (54.0)	37 (69.8)	0.081
ACEI/ARB, no. (%)	10 (15.9)	6 (11.3)	0.479
NSAID, no. (%)	4 (6.3)	7 (13.2)	0.209
Aminoglycoside, no. (%)	4 (6.3)	3 (5.7)	1.000[b]
Piperacillin/tazobactam, no. (%)	4 (6.3)	1 (1.9)	0.374
IV Contrast, no. (%)	26 (41.3)	21 (39.6)	0.857
Vancomycin Treatment Data			
Initial SCr (mg/dL), mean ± SD	1.12 ± 1.05	1.20 ± 0.78	0.649[a]
Vancomycin Indication			
SSTI, no. (%)	9 (14.3)	7 (13.2)	0.867
Osteomyelitis, no. (%)	2 (3.2)	3 (5.7)	0.659[b]
Pneumonia, no. (%)	31 (49.2)	30 (56.6)	0.427
Bacteremia, no. (%)	17 (27.0)	11 (20.8)	0.435
Vancomycin Duration (days), mean ± SD	8.2 ± 4.3	9.0 ± 6.1	0.397[a]
Nephrotoxicity, no. (%)	3 (4.8)	19 (35.8)	<0.001[*]

[*] *P*-value was <0.05

[a] *P*-value was calculated using independent t-test.

[b] *P*-value was calculated using Fisher's exact test due to one or more expected values being <5. All other *p*-values were calculated using chi-square test.

Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; ASCVD, atherosclerotic cardiovascular disease; ICU, intensive care unit; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; SSTI, skin and soft tissue infection; SCr, serum creatinine.

Obese Patients

Of the 336 patients, 111 (33.0%) patients were identified to be obese and had a mean BMI of 38.2 kg/m^2 (SD, 9.2 kg/m^2). The CART analysis showed that incidence of nephrotoxicity was significantly higher for obese patients with AUC_{24h} values greater than 586 mg*h/L (25.8% vs. 2.5%; p<0.001) (**Figure 5**).

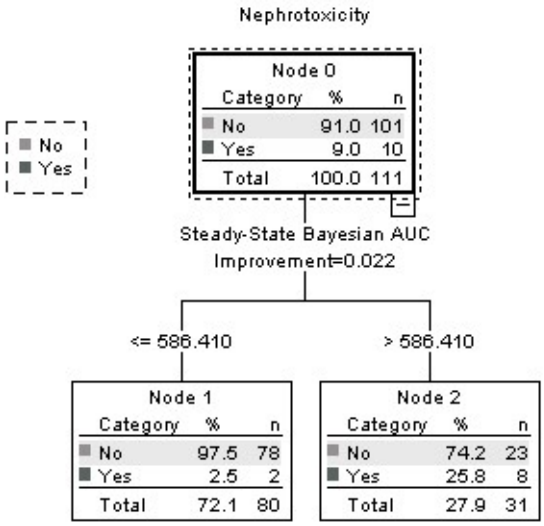

Figure 5. CART-derived AUC_{24h} nephrotoxicity threshold for obese patients.

Table 12, **Table 13**, and **Figure 6** show no statistical difference between the predictive performances of the CART-derived threshold and guideline threshold. No statistical differences were found between their PPVs (p=0.968), NPVs (p=0.357), sensitivities (p=0.317), and specificities (p=0.083). Additionally, the two thresholds had a difference in areas under the ROC curves of 0.035 (4.7%) and their overall predictive performances were noninferior to one another (0.786 vs. 0.751; p=0.488).

Table 12

Predictive Performances of CART-Derived AUC_{24h} Threshold and Guideline Threshold for Obese Patients

Predictive Performance	AUC_{24h} 586 mg*h/L	AUC_{24h} 600 mg*h/L	*P*-value
PPV (%)	25.8	25.9	0.968[a,c]
NPV (%)	97.5	96.4	0.357[a,d]
Sensitivity (%)	80.0	70.0	0.317[b,e]
Specificity (%)	77.2	80.2	0.083[b,f]
Area under ROC Curve (95% CI)	0.786 (0.635–0.938)	0.751 (0.579–0.923)	0.278[g]

[a] *P*-value was calculated using generalized score statistic.

[b] *P*-value was calculated using McNemar test.

[c] PPV data derived from 58 observations (31 patients with AUC_{24h} >586 mg*h/L and 27 patients with AUC_{24h} >600 mg*h/L).

[d] NPV data derived from 164 observations (80 patients with AUC_{24h} <586 mg*h/L and 84 patients with AUC_{24h} <600 mg*h/L).

[e] Sensitivity data derived from 10 nephrotoxic patients.

[f] Specificity data derived from 101 non-nephrotoxic patients.

[g] ROC analysis derived from 111 patients.

Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

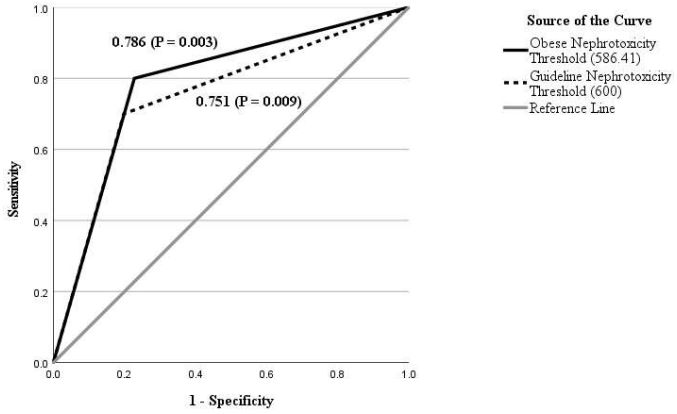

Figure 6. Receiver operating characteristic (ROC) curves of CART-derived AUC_{24h} threshold and guideline AUC_{24h} threshold for obese patients.

Table 13
AUC_{24h} of Obese Patients Who Experienced Nephrotoxicity

	AUC_{24h} ≤600 mg*h/L	**AUC_{24h} >600 mg*h/L**
AUC_{24h} ≤586 mg*h/L	2 (20.0)	0 (0)
AUC_{24h} >586 mg*h/L	1 (10.0)	7 (70.0)

P-value=0.317 (based on McNemar test); *n*=10
Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours.

The bivariate comparison of obese patients with AUC_{24h} values less than or equal to 586 mg*h/L versus those with AUC_{24h} values greater than 586 mg*h/L is displayed in **Table 14**. No confounding factors that can impact the risk of vancomycin-associated nephrotoxicity between the two groups were found.

Table 14

Patient Characteristics Between Obese Patients with AUC_{24h} Above and Below CART-Derived AUC_{24h} Threshold

Characteristic	AUC_{24h} ≤586.4 mg*h/L (*n*=80)	AUC_{24h} >586.4 mg*h/L (*n*=31)	*P*-value
Demographics			
Age (years), mean ± SD	54.1 ± 15.0	57.8 ± 9.0	0.201[a]
Male, no. (%)	67 (83.8)	26 (83.9)	0.988
BMI (kg/m^2), mean ± SD	37.7 ± 8.6	43.2 ± 14.0	0.071[a]
Selected Comorbidities			
Preexisting Liver Disease, no. (%)	12 (15.0)	7 (22.6)	0.341
ASCVD, no. (%)	12 (15.0)	4 (12.9)	1.000[b]
Heart Failure, no. (%)	8 (10.0)	7 (22.6)	0.119[b]
Diabetes, no. (%)	33 (41.3)	15 (48.4)	0.496
Hypertension, no. (%)	37 (46.3)	17 (54.8)	0.526
Selected Special Populations			
Critically Ill or ICU, no. (%)	28 (35.0)	10 (32.3)	0.785
Preexisting Renal Disease, no. (%)	12 (15.0)	11 (35.5)	0.017[a]
Concomitant Nephrotoxin, no. (%)			
Loop Diuretic, no. (%)	41 (51.2)	15 (48.4)	0.787
ACEI/ARB, no. (%)	21 (26.3)	6 (19.4)	0.447
NSAID, no. (%)	18 (22.5)	7 (22.6)	0.993
Aminoglycoside, no. (%)	4 (5.0)	1 (3.2)	1.000[b]
Piperacillin/tazobactam, no. (%)	2 (2.5)	1 (3.2)	1.000[b]
IV Contrast, no. (%)	40 (50.0)	14 (45.2)	0.647
Vancomycin Treatment Data			
Initial SCr (mg/dL), mean ± SD	1.13 ± 0.97	1.46 ± 0.83	0.102[a]
Vancomycin Indication			
SSTI, no. (%)	35 (43.8)	11 (35.5)	0.428
Osteomyelitis, no. (%)	10 (12.5)	3 (9.7)	1.000[b]
Pneumonia, no. (%)	23 (28.7)	7 (22.6)	0.511
Bacteremia, no. (%)	18 (22.5)	10 (32.3)	0.288
Vancomycin Duration (days), mean ± SD	6.8 ± 3.4	8.3 ± 7.7	0.141[a]
Nephrotoxicity, no. (%)	2 (2.5)	8 (25.8)	<0.001[*]

[*] *P*-value was <0.05

[a] *P*-value was calculated using independent t-test.

[b] *P*-value was calculated using Fisher's exact test due to one or more expected values being <5. All other *p*-values were calculated using chi-square test.

Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; ICU, intensive care unit; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; SSTI, skin and soft tissue infection; SCr, serum creatinine.

Patients with Preexisting Renal Disease

Of the 336 patients, 54 (16.1%) patients were considered to have preexisting chronic kidney disease or AKI upon admission. The CART analysis showed that incidence of nephrotoxicity was significantly higher for patients with AUC_{24h} values greater than 539 mg*h/L (31.2% vs. 0%; p=0.003) (**Figure 7**).

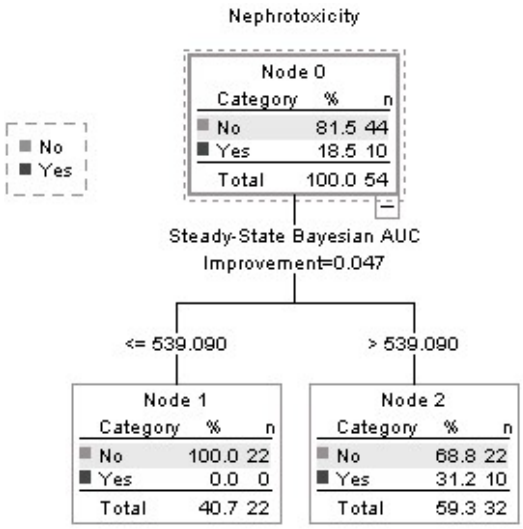

Figure 7. CART-derived AUC_{24h} nephrotoxicity threshold for patients with preexisting renal disease.

Table 15 and **Figure 8** compare the predictive performance of the CART-derived AUC_{24h} threshold and guideline threshold for patients with preexisting renal disease. The CART-derived threshold had a significantly higher NPV (p=0.025) and sensitivity (p=0.025). In other words, out of ten nephrotoxic patients with preexisting renal disease, the threshold of 539 mg*h/L identified five (50.0%) more nephrotoxic patients than the guideline threshold of 600 mg*h/L (**Table 16**). Although statistical significance was not achieved due to a small sample

size, the overall predictive performance of the 539 mg*h/L threshold was shown to be 0.148 (24.6%) higher than that of the 600 mg*h/L threshold (0.750 vs. 0.602; p=0.096).

Table 15
Predictive Performances of CART-Derived AUC_{24h} Threshold and Guideline Threshold for Patients with Preexisting Renal Disease

Predictive Performance	AUC_{24h} 539 mg*h/L	AUC_{24h} 600 mg*h/L	*P*-value
PPV (%)	31.3	27.8	0.653[a,c]
NPV (%)	100	86.1	0.025[a,d*]
Sensitivity (%)	100	50.0	0.025[b,e*]
Specificity (%)	50.0	70.5	0.003[b,f*]
Area under ROC Curve (95% CI)	0.750 (0.617–0.883)	0.602 (0.401–0.803)	0.096[g]

[*] *P*-value was <0.05
[a] *P*-value was calculated using generalized score statistic.
[b] *P*-value was calculated using McNemar test.
[c] PPV data derived from 50 observations (32 patients with AUC_{24h} >539 mg*h/L and 18 patients with AUC_{24h} >600 mg*h/L).
[d] NPV data derived from 58 observations (22 patients with AUC_{24h} <539 mg*h/L and 36 patients with AUC_{24h} <600 mg*h/L).
[e] Sensitivity data derived from 10 nephrotoxic patients.
[f] Specificity data derived from 44 non-nephrotoxic patients.
[g] ROC analysis derived from 54 patients.
Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

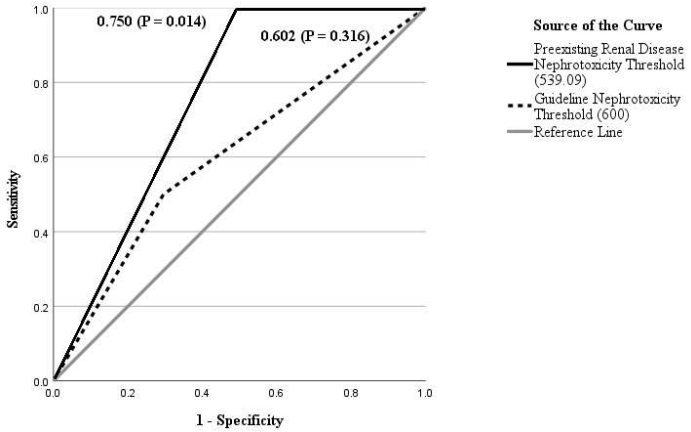

Figure 8. Receiver operating characteristic (ROC) curves of CART-derived AUC_{24h} threshold and guideline AUC_{24h} threshold for patients with preexisting renal disease.

Table 16
AUC_{24h} of Patients with Preexisting Renal Disease Who Experienced Nephrotoxicity

	AUC_{24h} ≤600 mg*h/L	**AUC_{24h} >600 mg*h/L**
AUC_{24h} ≤539 mg*h/L	0 (0)	0 (0)
AUC_{24h} >539 mg*h/L	5 (50.0)	5 (50.0)

P-value=0.025 (based on McNemar test); *n*=10
Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; ICU, intensive care unit.

Table 17 shows no confounding factors that can impact the risk of vancomycin-associated nephrotoxicity between the patients with AUC_{24h} values less than or equal to the CART-derived threshold and those with AUC_{24h} values above the CART-derived threshold.

Table 17

Patient Characteristics Between Patients with Preexisting Renal Disease with AUC_{24h} Above and Below CART-Derived AUC_{24h} Threshold

Characteristic	AUC_{24h} ≤539 mg*h/L (*n*=22)	AUC_{24h} >539 mg*h/L (*n*=32)	*P*-value
Demographics			
Age (years), mean ± SD	60.7 ± 12.3	65.0 ± 13.8	0.240[a]
Male, no. (%)	21 (95.5)	27 (84.4)	0.383[b]
Selected Comorbidities			
Preexisting Liver Disease, no. (%)	3 (13.6)	9 (28.1)	0.320[b]
ASCVD, no. (%)	9 (40.9)	8 (47.1)	0.216
Heart Failure, no. (%)	4 (18.2)	11 (34.4)	0.192
Diabetes, no. (%)	10 (45.5)	12 (37.5)	0.559
Hypertension, no. (%)	14 (63.6)	24 (75.0)	0.369
Selected Special Populations			
Critically Ill or ICU	9 (40.9)	14 (43.8)	0.836
Obese (BMI≥30 kg/m^2), no. (%)	7 (31.8)	15 (50.0)	0.184
Concomitant Nephrotoxin			
Loop Diuretic, no. (%)	14 (63.6)	16 (50.0)	0.322
ACEI/ARB, no. (%)	5 (22.7)	6 (18.8)	0.743[b]
NSAID, no. (%)	2 (9.5)	4 (12.5)	1.000[b]
Aminoglycoside, no. (%)	0 (0)	1 (3.1)	1.000[b]
Piperacillin/tazobactam, no. (%)	0 (0)	2 (6.3)	0.508
IV Contrast, no. (%)	4 (18.2)	4 (12.5)	0.702[b]
Vancomycin Treatment Data			
Initial SCr (mg/dL), mean ± SD	2.13 ± 1.53	1.94 ± 0.90	0.559[a]
Vancomycin Indication			
SSTI, no. (%)	6 (27.3)	14 (43.8)	0.218
Osteomyelitis, no. (%)	1 (4.5)	3 (9.4)	0.638[b]
Pneumonia, no. (%)	12 (54.5)	12 (37.5)	0.215
Bacteremia, no. (%)	3 (13.6)	5 (15.6)	1.000[b]
Vancomycin Duration (days), mean ± SD	7.0 ± 3.1	6.53 ± 3.5	0.613[a]
Nephrotoxicity, no. (%)	0 (0)	10 (31.3)	0.003[b*]

[*] *P*-value was <0.05

[a] *P*-value was calculated using independent t-test.

[b] *P*-value was calculated using Fisher's exact test due to one or more expected values being <5. All other *p*-values were calculated using chi-square test.

Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; ASCVD, atherosclerotic cardiovascular disease; ICU, intensive care unit; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; SSTI, skin and soft tissue infection; SCr, serum creatinine.

Patients on Concomitant Loop Diuretics

The CART-derived AUC_{24h} threshold for nephrotoxicity for the 126 (37.5%) patients on a concomitant loop diuretic was 543 mg*h/L. Incidence of nephrotoxicity was significantly higher for patients with AUC_{24h} values greater than 543 mg*h/L (34.5% vs. 2.9%; $p<0.001$) (**Figure 9**).

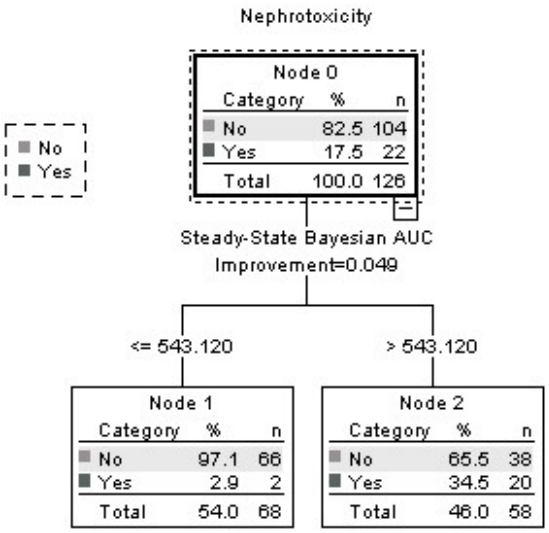

Figure 9. CART-derived AUC_{24h} nephrotoxicity threshold for patients on concomitant loop diuretics.

Table 18 and **Figure 10** provide the predictive performances of the CART-derived threshold and guideline threshold for patients on a concomitant loop diuretic. The CART-derived threshold had a significantly higher NPV ($p=0.028$) and sensitivity ($p=0.014$). In other words, out of 22 nephrotoxic patients on a concomitant loop diuretic, the threshold of 543 mg*h/L identified six (27.3%) more nephrotoxic patients than the guideline threshold (**Table 19**). Although statistical significance was not met due to the small sample size, the ROC curve

analysis showed that the CART-derived threshold's overall predictive performance was 0.055 (7.7%) higher than that of the guideline threshold (0.772 vs. 0.717; p=0.292).

Table 18
Predictive Performances of CART-Derived AUC_{24h} Threshold and Guideline Threshold for Patients on Concomitant Loop Diuretics

Predictive Performance	AUC_{24h} 543 mg*h/L	AUC_{24h} 600 mg*h/L	*P*-value
PPV (%)	34.5	40.0	0.235[a,c]
NPV (%)	97.1	91.2	0.028[a,d*]
Sensitivity (%)	90.9	63.6	0.014[b,e*]
Specificity (%)	63.5	79.8	<0.001[b,f*]
Area under ROC Curve (95% CI)	0.772 (0.677-0.867)	0.717 (0.591-0.844)	0.292[g]

[*] *P*-value was <0.05
[a] *P*-value was calculated using generalized score statistic.
[b] *P*-value was calculated using McNemar test.
[c] PPV data derived from 93 observations (58 patients with AUC_{24h} >543 mg*h/L and 35 patients with AUC_{24h} >600 mg*h/L).
[d] NPV data derived from 159 observations (68 patients with AUC_{24h} <543 mg*h/L and 91 patients with AUC_{24h} <600 mg*h/L).
[e] Sensitivity data derived from 22 nephrotoxic patients.
[f] Specificity data derived from 104 non-nephrotoxic patients.
[g] ROC analysis derived from 126 patients.
Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

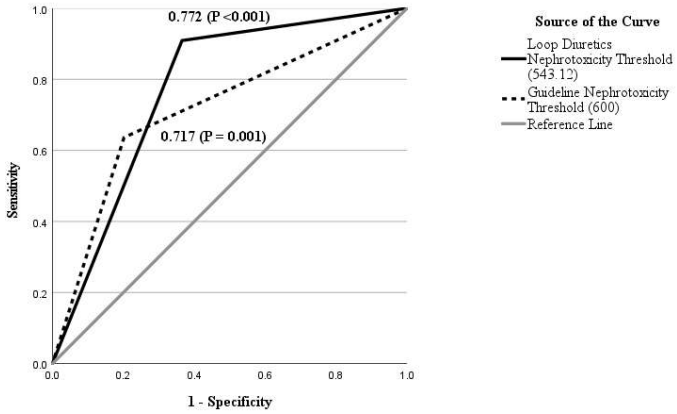

Figure 10. Receiver operating characteristic (ROC) curves of CART-derived AUC_{24h} threshold and guideline AUC_{24h} threshold for patients on concomitant loop diuretics.

Table 19
AUC_{24h} of Patients on Concomitant Loop Diuretics Who Experienced Nephrotoxicity

	AUC_{24h} ≤600 mg*h/L	**AUC_{24h} >600 mg*h/L**
AUC_{24h} ≤543 mg*h/L	2 (9.1)	0 (0)
AUC_{24h} >543 mg*h/L	6 (27.3)	14 (63.6)

P-value=0.014 (based on McNemar test); *n*=22
Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours.

No confounding factors were found when comparing patients on concomitant loop diuretics with AUC_{24h} values less than or equal to 543 mg*h/L to those with AUC_{24h} values greater than 543 mg*h/L (**Table 20**).

Table 20

Patient Characteristics Between Patients on Concomitant Loop Diuretics with AUC_{24h} Above and Below CART-Derived AUC_{24h} Threshold

Characteristic	AUC_{24h} ≤543 mg*h/L (*n*=68)	AUC_{24h} >543 mg*h/L (*n*=58)	*P*-value
Demographics			
Age (years), mean ± SD	58.9 ± 13.8	62.2 ± 14.8	0.189[a]
Male, no. (%)	63 (92.6)	14 (77.6)	0.016[*]
Selected Comorbidities			
Preexisting Renal Disease, no. (%)	14 (20.6)	16 (27.6)	0.358
Preexisting Liver Disease, no. (%)	15 (22.1)	9 (15.5)	0.351
ASCVD, no. (%)	17 (25.0)	14 (24.1)	0.911
Heart Failure, no. (%)	12 (17.6)	21 (36.2)	0.018[*]
Diabetes, no. (%)	25 (36.8)	14 (24.1)	0.126
Hypertension, no. (%)	37 (54.4)	34 (58.6)	0.635
Selected Special Populations			
Critically Ill or ICU, no. (%)	34 (50.0)	37 (63.8)	0.120
Obese (BMI≥30), no. (%)	34 (50.0)	22 (37.9)	0.174
Amputee, no. (%)	7 (10.3)	5 (8.6)	0.750
Vancomycin Treatment Data			
Initial SCr (mg/dL), mean ± SD	1.22 ± 1.03	1.29 ± 0.80	0.664[a]
Vancomycin Indication			
SSTI, no. (%)	16 (23.5)	16 (27.6)	0.602
Osteomyelitis, no. (%)	3 (4.4)	4 (6.9)	0.702[b]
Pneumonia, no. (%)	35 (51.5)	30 (51.7)	0.977
Bacteremia, no. (%)	16 (23.5)	10 (17.2)	0.385
Vancomycin Duration (days), mean ± SD	8.2 ± 4.0	9.1 ± 7.4	0.426[a]
Nephrotoxicity, no. (%)	2 (2.9)	20 (34.5)	<0.001[*]

[*] *P*-value <0.05

[a] *P*-value was calculated using independent t-test.

[b] *P*-value was calculated using Fisher's exact test due to one or more expected values being <5. All other *p*-values were calculated using chi-square test.

Abbreviations. AUC_{24h}, area under the concentration-time curve over 24 hours; ASCVD, atherosclerotic cardiovascular disease; ICU, intensive care unit; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; SSTI, skin and soft tissue infection; SCr, serum creatinine.

CHAPTER 5: DISCUSSION

This retrospective cohort study identified and examined the vancomycin AUC_{24h} thresholds for nephrotoxicity for critically ill patients, obese patients, patients with preexisting renal disease, and patients on concomitant nephrotoxins. It is the first study to perform analyses on vancomycin special populations to assess for AUC_{24h} thresholds for nephrotoxicity that differ from the guideline threshold of 600 mg*h/L. Compared to previous studies of a similar nature, this study adopted a less stringent definition of vancomycin-associated nephrotoxicity to capture more nephrotoxic patients.[8,12,32-36] Previous studies defined vancomycin-associated nephrotoxicity as an increase in SCr by 0.5 mg/dL or more or a 50% increase from baseline on two or more consecutive measures. On the other hand, this study adapted the definition of AKI from the 2012 KDIGO Clinical Practice Guideline for AKI and defined vancomycin-associated nephrotoxicity as an increase in SCr by 0.3 mg/dL or more within 48 hours or a 50% increase from baseline which is known or presumed to have occurred within seven days of discontinuing vancomycin.[37] Among the 336 patients included, 29 (8.6%) patients met the definition of nephrotoxicity. Consistent with prior studies' findings, an increased risk of nephrotoxicity was associated with critical illness, preexisting renal disease, higher initial serum creatinine levels, and concomitant loop diuretics.

Previous studies used various AUC parameters (e.g., $AUC_{0\text{-}24h}$, $AUC_{24\text{-}48h}$, and AUC_{24h}) and methods to assess their CART-derived AUC thresholds.[8,12,32-36] Prior to analyzing the special populations, the general population was analyzed to validate the method proposed in this study. For the general population, a CART-derived AUC_{24h} threshold of greater than 616 mg*h/L was significantly associated with an increased risk of nephrotoxicity. The difference in

predictive performances between the CART-derived threshold and guideline threshold was not statistically significant. No statistical differences were detected between the two thresholds' PPVs, NPVs, sensitivities, and areas under the ROC curves. Because the threshold of 616 mg*h/L was consistent with preexisting literature, the proposed method to estimate the CART-derived AUC_{24h} thresholds for nephrotoxicity and to assess their predictive performances was validated.

Although PPV, NPV, sensitivity, and specificity were estimated, PPV and sensitivity were given greater weight when determining the threshold for nephrotoxicity with the optimal predictive performance. For predicting nephrotoxicity, a higher PPV increases the likelihood of identifying patients with vancomycin exposures that result in nephrotoxicity. In addition, a higher sensitivity increases the accuracy of the AUC_{24h} threshold in detecting a true positive for nephrotoxicity and decreases the probability of having a false negative.

Critically ill patients frequently need larger doses of vancomycin due to their high acuity and their typically more resistant pathogens.[13,41] Additionally, they are more inclined to have hemodynamic instability, renal hypoperfusion, and an increased V_d of vancomycin that can increase their risk of nephrotoxicity. ICU residence and high APACHE II scores are independently associated with an increased risk of nephrotoxicity (aOR, 3.25; 95% CI, 1.18-9.98; p=0.02 and 22.9 ± 7.4 vs. 18.2 ± 8.5; p=0.006, respectively).[16,33] In this study, a CART-derived threshold of 544 mg*h/L was identified for critically ill patients. Compared to the guideline threshold, the CART-derived threshold had a similar PPV and a significantly higher sensitivity. Therefore, this study demonstrates that a lower vancomycin AUC_{24h} threshold than the guideline threshold of 600 mg*h/L should be considered in critically ill patients to decrease the risk of nephrotoxicity.

Currently, there are conflicting studies on the relationship between obesity and the risk of nephrotoxicity. Davies et al. did not associate obesity with an increased risk of nephrotoxicity (RR, 0.98; 95% CI, 0.93-1.04; p=0.59).[45] The current study also did not associate obesity with an increased risk of nephrotoxicity (32.9% vs. 34.5%, p=0.862). However, other studies have shown weight to be associated with an increased risk of nephrotoxicity (OR, 1.02; 95% CI, 1.00-1.03) and weight greater than 100 kg was an independent predictor of nephrotoxicity (OR, 2.74; 95% CI, 1.27-5.91).[14,15] Researchers hypothesize that the increased risk of nephrotoxicity is due to obese patients having an increased V_d of vancomycin that leads to disproportionately larger doses and a more intensive vancomycin exposure profile.[42,43] However, the AUC_{24h} parameter already accounts for vancomycin dosing and is directly proportional to the amount of vancomycin administered. Thus, even if obesity is associated with an increased risk of nephrotoxicity, the AUC_{24h} threshold for nephrotoxicity is suspected to not be lowered in obese patients. In this study, a significant CART-derived threshold was not identified for obese patients. Compared to the guideline threshold, the CART-derived threshold of 586 mg*h/L did not have a statistically significant PPV, NPV, sensitivity, specificity, or area under the ROC curve. Therefore, this study supports the continued use of 600 mg*h/L as the AUC_{24h} threshold for nephrotoxicity in obese patients.

Studies have shown that patients with preexisting renal disease are associated with a higher risk of nephrotoxicity as vancomycin is predominantly eliminated renally.[17,20] A significant CART-derived threshold of 539 mg*h/L was identified in patients with preexisting renal disease. Compared to the guideline threshold, the AUC_{24h} threshold of 539 mg*h/L had a comparable PPV and a significantly higher sensitivity. To minimize the risk of vancomycin-

associated nephrotoxicity, this study supports using a lower vancomycin AUC_{24h} threshold than the guideline threshold of 600 mg*h/L in patients with preexisting renal disease.

A prospective study determined that patients on concomitant nephrotoxins were significantly associated with an increased risk of nephrotoxicity (91% vs. 20%; $p<0.001$).[19] Concomitant nephrotoxins remained a significant predictor of nephrotoxicity after performing a multivariate analysis ($p=0.003$). Concomitant loop diuretics increase the risk of vancomycin-associated nephrotoxicity by 43-fold.[18] The current study identified a significant CART-derived threshold of 543 mg*h/L for patients on concomitant loop diuretics. The CART-derived threshold had a comparable PPV but a significantly higher sensitivity compared to the guideline threshold. For patients on concomitant loop diuretics, a lower vancomycin AUC_{24h} threshold than the guideline threshold of 600 mg*h/L should be considered to minimize the risk of nephrotoxicity.

Other concomitant nephrotoxins such as renin-angiotensin system blockers, NSAIDs, aminoglycosides, piperacillin-tazobactam, and IV contrast dyes have also demonstrated synergistic activity with vancomycin in the development of nephrotoxicity.[18,20,48-50] However, less than ten nephrotoxic patients were observed and therefore CART analysis was not performed in these special populations. With the exception of patients on IV contrast dyes, these special populations had less than ten nephrotoxic patients due to their small sample sizes. Despite having an adequate sample size of patients who received IV contrast dyes, less than 10 nephrotoxic patients were observed. This was hypothesized to be due to patients commonly receiving sodium bicarbonate or acetylcysteine prior to receiving IV contrast dyes at SJGH to minimize the risk of nephrotoxicity. Further research is needed to determine if the upper AUC_{24h}

threshold is consistent or varies when used in patients on concomitant ACEIs, ARBs, NSAIDs, aminoglycosides, piperacillin-tazobactam, or IV contrast dyes.

The CART-derived thresholds identified for critically ill patients, patients with preexisting renal disease, and patients on concomitant loop diuretics are inherently able to provide AUC_{24h} thresholds where the risk of nephrotoxicity is most disproportionate. However, studies theorize that the incidence of vancomycin-associated nephrotoxicity increases along the AUC_{24h} continuum.[4] Therefore, it is important to recognize that the study's findings of AUC_{24h} thresholds that are lower than the guideline threshold serve as a guidance for clinicians to be cognizant of the potential synergistic nephrotoxicity risk when dosing vancomycin in special populations such as critically ill patients, patients with preexisting renal disease, and patients on concomitant loop diuretics. Clinicians should consider dosing vancomycin more conservatively in these special populations.

Study Limitations

The current study has several limitations that are mostly inherent to the study's single-center, retrospective study design. Foremost, a majority of the patients were male and Caucasian. However, no study has reported significantly different AUC_{24h} thresholds for nephrotoxicity based on gender or race. Based on statistical analysis using this study's population, the incidence of nephrotoxicity was not significantly different between males and females (p=0.828) and between Caucasians and non-Caucasians (p=0.145). Therefore, the dominant male and Caucasian population may not limit the application of the current study to females or other races.

Moreover, not all of the patients included in the nephrotoxicity analysis had *Staphylococcus aureus* infections. Patients on vancomycin due to suspected MRSA but then

finalized with other gram-positive or gram-negative pathogens were still included in the nephrotoxicity analysis. However, the inclusion of non-MRSA infections was considered appropriate as the main endpoint measurement was nephrotoxicity rather than efficacy of the drug exposure. In addition, it mimics real-life clinical practice settings where causative pathogens are commonly yet to be identified during the initial course of vancomycin.

Additionally, trough concentrations were primarily used to estimate the Bayesian-derived AUC_{24h} rather than both peak and trough concentrations. However, Ho et al. demonstrated significant correlations between the Bayesian-derived AUC_{24h} values estimated from one sample and those from two samples (p <0.001).[53] Therefore, the CART-derived AUC_{24h} thresholds derived from predominately trough concentrations would not be meaningfully different from those derived from peak and trough concentrations.

Lastly, this study did not include the AUC_{24h}/MIC_{BMD} threshold for efficacy of vancomycin. This outcome had been planned in the early state of the research and the study initially aimed to identify the CART-derived AUC_{24h}/MIC_{BMD} thresholds associated with treatment success in MRSA-associated infections and special populations such as critically ill patients, amphetamine users, IVDU, and patients on concomitant immunosuppressants. However, only 13 (3.9%) patients had clinical failure. Furthermore, only 81 (24.3%) patients were isolated with MRSA and 17 (21.0%) of those patients had AUC_{24h}/MIC_{BMD} ratios less than 400. Therefore, this study focused only on the AUC_{24h} threshold for nephrotoxicity.

Future Directions

As more hospitals continue to transition from trough-based monitoring to AUC_{24h}-based monitoring, further studies should be conducted to establish a relationship between the vancomycin AUC_{24h} threshold for nephrotoxicity and special populations such as critically ill

patients, obese patients, patients with preexisting renal disease, and patients on concomitant nephrotoxins. Additional studies should also be conducted to assess the impact on the AUC_{24h} threshold when patients meet the description of more than one special population.

A follow-up multicenter, prospective study is warranted to validate the lower CART-derived AUC_{24h} that was identified in critically ill patients, patients with preexisting renal disease, and patients on concomitant loop diuretics. The impact on the AUC_{24h} threshold when patients meet the description of more than one special population should also be considered. Furthermore, conducting the study at multiple institutions can increase the sample size of the study. Having more nephrotoxic patients in each special population can improve the estimation of the CART-derived thresholds for nephrotoxicity and the assessment of their predictive performances. Additionally, it will allow further analyses on special populations that the current study was unable to analyze (e.g., patients on concomitant ACEIs, ARBs, NSAIDs, aminoglycosides, piperacillin-tazobactam, or IV contrast dyes). Moreover, collecting both peak and trough concentrations would be ideal to maximize the accuracy of estimating the AUC_{24h}. Additional parameters can also be collected to better describe the special populations. For example, a scoring system such as the APACHE II can be used to stratify critically ill patients based on the severity of their critical illness. Similarly, recording the dose and duration of the concomitant nephrotoxins can help determine if conservative vancomycin dosing needs to be considered in patients who receive a single dose or low doses of a concomitant nephrotoxin.

A multicenter, prospective study is also needed to investigate the generalizability of the proposed vancomycin AUC_{24h}/MIC_{BMD} threshold of 400 for clinical efficacy in different MRSA-associated infections and vancomycin special populations. This will ensure that the study is

adequately powered and includes enough incidences of MRSA infections and clinical failures to estimate the CART-derived thresholds for clinical efficacy.

CHAPTER 6: CONCLUSION

For critically ill patients, patients with preexisting renal disease, and patients on concomitant loop diuretics, a lower vancomycin AUC_{24h} threshold for nephrotoxicity such as 544 mg*h/L, 539 mg*h/L, and 543 mg*h/L, respectively, may be considered to minimize the risk of nephrotoxicity. Compared to the vancomycin AUC_{24h} threshold of 600 mg*h/L that is currently recommended by the 2020 ASHP/IDSA/PIDS/SIDP updated vancomycin monitoring guideline, these thresholds had comparable PPVs but significantly higher sensitivities. On the other hand, this study supports the continued use of the vancomycin AUC_{24h} threshold of 600 mg*h/L to minimize the risk of nephrotoxicity in obese patients.

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