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Precision Drug Delivery for Vancomycin Efficacy and Safety in Critically Ill Patients

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PRECISION DRUG DELIVERY FOR VANCOMYCIN EFFICACY AND SAFETY IN CRITICALLY ILL PATIENTS

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Medicine at the University of Kentucky

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ABSTRACT OF DISSERTATION

PRECISION DRUG DELIVERY FOR VANCOMYCIN EFFICACY AND SAFETY IN CRITICALLY ILL PATIENTS

Vancomycin is the most commonly prescribed antibiotic for hospitalized patients. Despite this fact and decades of clinical use, clinicians remain challenged to meet dosing targets of this narrow therapeutic index drug as well as minimize the risks of therapy, primarily nephrotoxicity. These concerns are magnified in critically ill patients given their severity. Accordingly, in a series of five clinical studies, we sought to identify optimal methods of vancomycin administration in critically ill patients to maximize efficacy and minimize nephrotoxicity via three techniques: use of continuous versus intermittent infusion, use of first-dose pharmacokinetic calculations to guide dosing, and use of loading doses. (1) To identify the landscape in which vancomycin is being used, we surveyed critical care pharmacists on self-reported vancomycin dosing practices. Ninety four percent (94.2%) of pharmacists reported rarely using continuous infusions and 89.2% rarely using first-dose pharmacokinetic evaluation. Loading doses were more commonly used, but rationale for not using included lack of evidence and concern for acute kidney injury (AKI). (2) Given this hesitation by clinicians, we performed a retrospective cohort study of 449 critically ill patients with confirmed methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia and/or bacteremia to test the association of a loading dose of vancomycin (≥ 20 mg/kg) with clinical failure. While we found no difference in clinical failure with use of a loading dose versus not, we also found no difference in AKI. (3) Given that few clinicians reported using first-dose pharmacokinetic evaluation to guide dosing, we performed a retrospective cohort study of 66 critically ill patients to test if first-dose pharmacokinetic evaluation was associated with greater area-under-the-curve (AUC) target attainment at steady state. Indeed, first-dose pharmacokinetic evaluation increased AUC target attainment to 58.6% compared to 32.4% (p=0.033) in those patients who received empiric dosing. (4) Method of infusion may also impact AKI risk in critically ill patients. We performed a systematic review and meta-analysis of vancomycin continuous versus intermittent infusion in critically ill patients. Eleven studies were identified which evaluated 2,123 patients. The risk of AKI was found to be significantly reduced in continuous compared to intermittent infusion: odds ratio 0.47 [95% confidence interval (CI) 0.34-0.65]. Additionally, continuous infusions were associated with 2.63 greater odds (95% CI 1.52-4.57) of pharmacokinetic

target attainment compared to intermittent infusion. (5) In order to build from the theme that continuous infusions offer more precise dosing at a lower risk of AKI, we conducted a prospective observational study of 50 critically ill patients receiving continuous infusion vancomycin that consisted of 239 dosing events and 124 vancomycin concentrations. A population pharmacokinetic model was constructed to guide further precision dosing in future studies of continuous infusion vancomycin. These findings support further investigation of early pharmacokinetic evaluation and use of continuous infusions to maximize the precision of vancomycin delivery to critically ill patients and minimize the risk of AKI. Additionally, this work's blueprint provides an approach for future study of precision dosing of antimicrobials in critically ill patients.

KEYWORDS: Vancomycin, Pharmacokinetics, Acute Kidney Injury, Dosing, Critical Care, Continuous Infusion

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April 20, 2021
Date

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To my parents, for instilling in me the value of education, and my wife, Shannon, and my children, Harrison and Makena, for always reminding me where life's priorities lie.

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In addition, my critical care pharmacy and physician colleagues contributed to collaborations vital to the execution of this work. I look forward to our future collaborations, learning as much as we can from the patients we care for today, in order to offer the absolute most-informed care we can tomorrow.

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CHAPTER 1 INTRODUCTION

1.1 Epidemiology of MRSA Infection and Vancomycin Use in Critically Ill Patients

Vancomycin is the most commonly prescribed antibiotic for hospitalized patients in the United States, with reports demonstrating increasing use over time.[1-4] Using estimates of 36.5 million hospital stays annually in the United States,[5] and approximately 100 days of therapy per 1000 patient-days,[3,4] it has been estimated that over 3 million patients receive vancomycin every year in the United States alone.[6]

Vancomycin is primarily used to treat *Staphylococcus aureus*, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA is responsible for a wide variety of infections in hospitalized patients, including bloodstream infections, pneumonia, device-related infections, skin and soft tissue infection, and others.[7] In a nationwide surveillance study of United States hospitals over a seven year period, *Staphylococcus aureus* was responsible for 20% of nosocomial bloodstream infections, with an alarming increase in MRSA isolates more than doubling from 22% to 57% over the period from 1995-2001.[8] In critically ill patients, MRSA bacteremia was associated with significantly higher attributable mortality compared to methicillin-sensitive *Staphylococcus aureus* (MSSA).[9] *S. aureus* is isolated in approximately one out of every five cases of ventilator-associated pneumonia, with approximately 56% MRSA isolates.[10]

Vancomycin was approved by the Food and Drug Administration (FDA) in 1958,[11] yet despite additional antimicrobials garnering FDA approval, it remains one of the most commonly used antibiotics for MRSA, particularly in critically ill patients. A tricyclic glycopeptide, vancomycin is bactericidal by binding to D-alanyl D-alanine, which subsequently inhibits synthesis and polymerization of N-acetylmuramic acid and N-acetylglucosamine, long polymers that make up the peptidoglycan cell wall layer.[12] In

national guidelines for a variety of conditions impacting critically ill patients, it remains as a primary recommendation for empiric or definitive therapy for several conditions when MRSA infection is suspected or confirmed, including: sepsis,[13] pneumonia,[14] meningitis,[15] catheter-associated bloodstream infections,[16] intra-abdominal infections,[17] neutropenic fever,[18] endocarditis,[19] and skin and soft tissue infections,[20] among others. Other potential antimicrobials against MRSA have known limitations that may limit use. Daptomycin is inactivated by pulmonary surfactant thus not suitable for treating pneumonia,[21] a common source of infection on the differential diagnosis for critically ill patients with sepsis and unknown foci of infection. Limited data, particularly randomized controlled trials, exist for ceftaroline in the above-mentioned conditions. Linezolid has been compared to vancomycin, but meta-analyses suggest no benefit of linezolid in terms of mortality, clinical response, or safety.[22] In addition, the direct drug costs of these therapies often far exceed vancomycin. Antimicrobial stewardship concerns have curtailed use of other antibiotics against MRSA given limited alternative therapeutic options available for widespread use against MRSA should vancomycin lose sufficient activity against MRSA to be used for empiric therapy. As such, despite the challenges of using vancomycin for MRSA infections, it remains the most common choice for empiric or definitive antibiotic therapy for MRSA in most centers in the United States healthcare system.

1.2 Need for Precision Vancomycin Dosing in Critically Ill Patients

Despite FDA approval for over 50 years, active investigation continues into the optimal dosing, monitoring, and administration strategies for vancomycin, as evidenced by a recent change in national guidelines from trough-based to area-under-the-curve

(AUC)-based dosing, a paradigm shift in how vancomycin is monitored in the clinical setting.[23] In particular, critically ill patients have arguably the greatest need for precision dosing of vancomycin for several reasons. First, due to life-threatening infections present in the intensive care unit (ICU) patient population, rapid and sustained attainment of pharmacokinetic/pharmacodynamic (PK/PD) targets with antimicrobials likely offers greater benefit in critically ill patients compared to less ill patient populations. Second, vancomycin is already a known narrow therapeutic index drug, and critically ill patients are known to have alterations impacting hydrophilic antibiotics such as vancomycin including altered volumes of distribution (V_d) and clearance (CL).[24] Finally, patients in the ICU have multiple non-modifiable risk factors for acute kidney injury (AKI), and severity of illness is an acknowledged risk factor for vancomycin nephrotoxicity.[25] In short, critically ill patients have the most to gain from precision dosing of vancomycin for efficacy and the narrowest margin for error with nephrotoxicity.

1.3 AUC:MIC Ratio as the Pharmacokinetic/Pharmacodynamic Target

As mentioned, the most recent consensus statement for vancomycin dosing and monitoring recommends a shift from trough-based dosing to AUC monitoring. Specifically, an area-under-the curve to minimum inhibitory concentration (AUC/MIC) ratio ≥ 400 is the recommended PK/PD efficacy target.[23] A few caveats deserve mention on this topic prior to proceeding. First, this AUC/MIC recommendation primarily originates from *in vitro* and *in vivo* experiments,[26-30] with some supporting observational clinical data,[31,32] and failure to attain this AUC/MIC ratio may be associated with the emergence of MRSA resistance to vancomycin.[33] Second, this AUC/MIC typically refers to MIC as that determined by broth microdilution (BMD). Commercially available MIC

testing methods are highly variable, both among themselves and the reference BMD.[34] Furthermore, given that the BMD MIC_{90} is reportedly ≤ 1 mg/L in most institutions,[35] consensus guidelines recommend assuming an MIC of 1 mg/L unless otherwise known to be higher.[23] This simplifies the vancomycin dosing target in practice to a pharmacokinetic target, rather than a PK/PD target. Third, although a change from trough-based dosing to AUC-based dosing has been associated with reduced nephrotoxicity,[36] the upper limit of vancomycin AUC remains debated from the standpoint of nephrotoxicity risk. A number of studies, including a meta-analysis, have found AUC values slightly above 600 mg·hr/L as a critical threshold for additional nephrotoxicity risk.[37] Accordingly, the recommended pharmacokinetic target for clinical use of vancomycin is 400-600 mg·hr/L.[23]

1.4 Specific Aims

Against this backdrop of evolving evidence of vancomycin use, my dissertation work is aimed at studying three techniques to optimize the efficacy and safety of vancomycin dosing in critically ill patients: loading doses, first-dose pharmacokinetic evaluation, and continuous infusions.

1.4.1 Aim 1: To establish current dosing and monitoring practices regarding vancomycin use in critically ill patients. This will be accomplished via an online survey of practicing critical care pharmacists in adult critical care and sponsored by the pharmacy section of a multidisciplinary critical care organization. We will aim to establish critical care pharmacist self-reported compliance with the 2009 vancomycin guidelines as well as other nuances of vancomycin dosing and monitoring,[38] with particular survey items addressing areas of interest to this dissertation, including loading doses, first-dose

pharmacokinetic evaluation, and continuous infusions, among others. We will also survey clinical practitioners on a group of hypothesized best practices for vancomycin dosing in critically ill patients that, while considered important by the research team, may not have had sufficient space in vancomycin consensus documents to comment on. This introductory study will serve to assess the clinical landscape of vancomycin dosing and monitoring in critically ill patients in current times. Based on a survey of infectious disease pharmacists from nearly 10 years ago,[39] we anticipate non-universal adoption of loading doses of vancomycin. This prior survey[39] identified a critical need to uncover clinician rationale for non-compliance with guideline recommendations, which we plan to address by not only asking about a variety of clinical scenarios for loading doses but also by asking pharmacists why they may not always use such an option. Commonly noted clinician hesitations will be considered in our clinical design of aim 2 assessing loading doses. Given the timing of the survey administration, we anticipate that few institutions are early adopters of AUC-guided dosing and that few pharmacists report using first-dose pharmacokinetic evaluation. Given the 2009 vancomycin guideline's recommendation that "continuous infusions are unlikely to substantially improve patient outcome when compared with intermittent dosing"[38] we also anticipate finding that few pharmacists are using continuous infusions of vancomycin, which we anticipate serving as important baseline preliminary data, and establishing the need for change efforts, should we identify continuous infusions of vancomycin reduce AKI compared to intermittent infusion.

1.4.2 Aim 2: To assess the clinical benefit of a vancomycin loading dose in critically ill patients with MRSA infection. Optimizing vancomycin use in critically ill patients starts

with the first dose, and given the increased V_d in critically ill patients, it is highly likely that critically ill patients require loading doses to produce sufficient serum concentrations to meet identified AUC/MIC goals. The 2020 vancomycin guidelines offer that a loading dose of 20-35 mg/kg actual body weight (up to 3,000mg) can be administered to critically ill patients with suspected or confirmed MRSA infection in order to more rapidly attain target serum concentrations; however, this recommendation is only supported by moderate evidence (BII; B- moderate evidence to support a recommendation for or against use, II- evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from more than 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments).[23] Producing clinical evidence of benefit is challenging in any condition, but if there is a patient population of MRSA infections that would benefit from a loading dose, critically ill patients would appear to be highly likely as they are most at risk of poor outcomes from infection. In 2015, myself and another collaborator wrote a grant proposal to the Critical Care Pharmacotherapy Trials Network for a randomized, controlled trial of loading doses on pharmacokinetic target attainment and AKI, but valid concerns were noted in the review process of the extremely narrow time window allotted for informed consent in these situations of sepsis, where every hour delay in antimicrobial therapy within the first six hours is associated with a 7.6% reduction in survival.[40] Additionally, the number of patients that would have to be enrolled to accrue a sufficient number of patients with documented MRSA cultures, and thus any sufficiently powered study of efficacy, would make the sample size infeasible. As such, it became clear that the most likely way to study clinical efficacy of loading doses was destined to

be a cohort study. If we want clinicians to use loading doses, and if part of the reason they tell us they are not (which will be assessed in Aim 1) is due to lack of clinical efficacy data, then it is imperative to provide this evidence.

1.4.3 Aim 3: To compare an approach of first-dose pharmacokinetic evaluation with empiric dosing of vancomycin on AUC target attainment at steady state in critically ill patients. Even though we now have clear guidance on the AUC goal of 400-600 mg·hr/L, it was clear to myself and practicing colleagues in the critical care units that our empiric approach to dosing vancomycin was often insufficient. Whenever vancomycin concentrations were assessed at steady state, we commonly found trough or AUC values outside of our target range. While nomograms of varying accuracy for vancomycin have existed for years, what could represent more of a personalized approach to dosing than assessing serum concentrations after a single dose and using a patient's own pharmacokinetic response to develop more precise future dosing regimens? This approach of first-dose pharmacokinetic evaluation, indeed, has been studied for aminoglycosides[41] and incorporated into clinical practice in certain scenarios. In revising our institution's vancomycin dosing guidance, use of first-dose pharmacokinetic evaluation was added as an approved option for pharmacists dosing vancomycin, and particularly adopted in the medical ICU. The first-dose pharmacokinetic evaluation concept has previously been evaluated to a limited extent in adult and pediatric populations with mixed results.[42,43] As they relate to vancomycin, prior studies evaluated target attainment as trough rather than the currently recommended AUC. Accordingly, no data exist on whether first-dose pharmacokinetic evaluation of vancomycin improves AUC target attainment at steady state. Given our institution's stance as an early adopter

of AUC-guided vancomycin dosing, unique pharmacy practice model, and history of a robust therapeutic drug monitoring program, we are primed to study this issue assessing utility of first-dose pharmacokinetic evaluation, particularly in a targeted population of critically ill patients with wide variability in pharmacokinetic alterations. Following study of loading doses and first-dose pharmacokinetic evaluation, we will turn attention to the method of administration and focus on infusion strategy as a mechanism for precision dosing and maximizing safety.

1.4.4 Aim 4: To perform a systematic review and meta-analysis on the risk of AKI in critically ill adults with continuous versus intermittent infusion of vancomycin. As noted earlier, AUC values routinely above 600 mg·hr/L have been associated with nephrotoxicity.[37] Given their correlation, it is no surprise that vancomycin trough and peak concentrations have similarly been associated with nephrotoxicity to some extent.[44,45] Data from animal models suggest that AUC or C_{max}, but not trough, drive the nephrotoxicity of vancomycin as assessed by urinary kidney biomarkers of injury kidney injury molecule-1 (KIM-1) and osteopontin.[6] Furthermore, in the same animal model, the previous investigators also showed that equivalent vancomycin doses given less frequently (once or twice daily administration, thus higher peak levels of the drug, compared to three or four times daily), showed higher levels of urinary KIM-1.[46]

Vancomycin's nephrotoxicity has long been known, but the precise mechanisms of toxicity remain debated.[25] One proposed mechanism of toxicity includes disruption of mitochondrial function and production of reactive oxygen species, particularly in the proximal tubule cells of the kidney.[47] Supporting this hypothesis, multiple antioxidants have shown promise of reducing vancomycin nephrotoxicity in pre-clinical studies.[48]

Secondly, vancomycin is filtered at the glomerulus and is both secreted and reabsorbed by the proximal tubule cells.[49,50] Drugs such as cilastatin have been shown to block the reuptake of vancomyin by megalin, a major endocytic receptor on proximal tubule cells, and subsequently reduce the nephrotoxicity from vancomycin in pre-clinical models.[51] Third, a small series of biopsies from patients with confirmed vancomycin-associated nephrotoxicity (and with elevated vancomycin troughs) revealed obstructive tubular casts formed from non-crystal vancomycin aggregates in complex with uromodulin via an unknown mechanism.[52] Given these findings associated with vancomycin nephrotoxicity, hypothesized mechanisms for reduced kidney injury with continuous infusions compared to intermittent infusions may be related to the availability of drug for uptake into the proximal tubule. By avoiding the high peak concentrations, either accessible to the proximal tubule by the basolateral membrane or via reabsorption from the apical membrane from the tubular lumen of the proximal tubule cell, this may keep the proximal tubule cell's exposure to vancomycin below some critical threshold that initiates a series of events that alters mitochondrial function and cell proliferative response.[53] Complementary or alternatively, these higher peak concentrations may contribute to a saturation point that influences the cast nephropathy observed from human biopsy studies,[52] although less is known about this mechanism of toxicity.

Two smaller randomized controlled trials have previously studied continuous vs. intermittent infusions, however, a number of factors have changed since these studies, including vancomycin dosing targets (AUC vs. trough) as well as definitions for kidney injury with classifications over the years focusing on more sensitive definitions rather than a more severe state of kidney injury.[54,55] A number of observational studies have

been published comparing the two infusion strategies, however, meta-analyses have either not focused on critically ill patients in particular[56] or have applied meta-analytic techniques that pooled unadjusted data from studies rather than considering the adjusted estimates from individual studies.[57] Given the smaller sample sizes of the pre-existing studies, a meta-analysis in this scenario can not only increase the overall sample size of patients considered, but also produces an informed prior estimate in terms of the effect size for planning of future comparative trials. Building from the meta-analysis, the final piece of the dissertation will focus on building a population pharmacokinetic model of continuous infusion vancomycin in critically ill patients.

1.4.5. Aim 5: Build a population pharmacokinetic model of continuous infusion vancomycin in critically ill adults. In preparing for future work comparing continuous versus intermittent infusions of vancomycin, it will be critical to ensure that dosing regimens are equally precise in both arms. While the focus of algorithms, nomograms, and Bayesian software programs has been on intermittent infusions, much less focus has been given to building models of continuous infusion vancomycin, presumably due to the low frequency of use with which we anticipate observing in Aim 1. It is unknown if vancomycin administered continuously differs in its pharmacokinetic behavior compared to intermittent infusion. While a systematic review and meta-analysis revealed that continuous infusions of vancomycin had greater pharmacokinetic target attainment and lower variability compared to intermittent infusion,[58] even with continuous infusions the pharmacokinetic target attainment rates were as low as 47-57% in some studies of critically ill patients.[54,59] As with first-dose pharmacokinetic evaluation, we incorporated continuous infusion administration of vancomycin as a dosing strategy while revising our

institutional vancomycin guidelines, again used primarily in the medical ICU. A prospective observational study of 50 patients will be planned based on guidance for number of subjects in population pharmacokinetic studies with sparse sampling,[60,61] and a population pharmacokinetic model built from these data. Monte-Carlo simulations will be performed with the hope of developing simplified dosing nomograms depending on the findings from our population model.

These five aims will allow for assessment of three different strategies for the difficult, but necessary task of precision dosing of vancomycin in critically ill patients. These series of studies are advantageous in that not only are they immediately applicable to direct clinical practice, but they will also serve as preliminary data for future study of optimizing vancomycin delivery to critically ill patients, in particular, further comparative effectiveness and urinary biomarker research between continuous and intermittent infusions.

CHAPTER 2 CURRENT VANCOMYCIN DOSING PRACTICES

Flannery AH, Hammond DA, Oyler DR, Li C, Wong A, Smith AP, Yeo Q, Chaney W, Pfaff CE, Plewa-Rusiecki AM, Juang P. Vancomycin Dosing Practices among Critical Care Pharmacists: A Survey of Society of Critical Care Medicine Pharmacists. *Infect Dis (Auckl)*. 2020 Sep 25;13:1178633720952078. doi: 10.1177/1178633720952078.

2.1 Introduction

From 2009-2020, guidelines for vancomycin dosing were available through a joint effort from the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP).[38] Despite availability of these guidelines and over 50 years of clinical experience, much remains unknown regarding the optimal use of vancomycin in clinical practice.[62] A 2013 survey of infectious diseases pharmacists revealed discordance between vancomycin practices and guideline recommendations, particularly regarding a reluctance to use loading doses in seriously ill patients, to use actual body weight for dose calculation in obesity, and to systematically monitor for complications such as nephrotoxicity.[39]

The compliance of pharmacists and physicians with guideline recommendations for vancomycin dosing and monitoring is important from an overall antimicrobial stewardship perspective, but is of particular importance in the critical care setting for several reasons. The complexities of the intensive care unit (ICU) patient population introduce additional challenges to a complex drug. The acuity of the patient population demands adequate pharmacokinetic-pharmacodynamic target attainment for serious, life-threatening infections while minimizing the risk of nephrotoxicity for patients already at risk of acute kidney injury and often simultaneously prescribed multiple other nephrotoxins. Critically ill patients' clearance of vancomycin could vary, from significant decreases in acute kidney injury to clinically significant increases in the setting of augmented renal clearance. Adjustments for other medical therapies, such as continuous renal replacement therapy (CRRT) and other dialysis modalities, represent unique

circumstances that may not be addressed by guidelines. Other 'best practice' items related to vancomycin dosing in the critically ill are likely variable across ICU pharmacists due to unique aspects of this patient population.

If any discordant areas of practice deviate in a substantial way from guideline recommendations, understanding factors driving critical care pharmacists' decisions to do so are important to elucidate and represent cornerstones of implementation science efforts. The purpose of this survey was to determine if this variability exists in an effort to potentially inform future guideline recommendations and to reduce variability in evidence-based practices. We sought to build on a prior survey of vancomycin use[39] in the following ways: 1. To perform a more recent survey of practice patterns given the continuously updated literature on vancomycin since 2013, 2. To study under which clinical scenarios ICU pharmacists may not adhere to guideline recommendations and ascertain why, 3.) To characterize practice patterns regarding ICU-centric dosing challenges that may not be addressed in consensus guidelines, and 4. To explore respondent characteristics associated with compliance to guideline recommendations or early adoption of certain vancomycin dosing practices.

2.2 Materials and Methods

2.2.1 Survey Design

A survey was developed by a pharmacist working group of the Society of Critical Care Medicine (SCCM) Clinical Pharmacy and Pharmacology (CPP) Research and Scholarship Committee in early 2017. This survey was approved by the University of Kentucky Institutional Review Board as an exempt study.

Survey questions were developed by the working group using the 2009 ASHP/IDSA/SIDP guidelines as a template.[38] Once guideline recommendations were addressed in the survey, the additional survey questions were created to capture additional areas of what the authors considered "best practice" or areas where substantial variability in practice was hypothesized to exist; for example, whether pharmacists were alerted to initiation or discontinuation of renal replacement therapies to adjust dosing accordingly. The survey was a 24-item questionnaire, with six general demographic questions, eight vancomycin-related demographic questions regarding the practice site, and 10 questions related to individual clinician's vancomycin dosing practices (**Appendix 1**).

A modified Likert scale was used: rarely (<10% of the time); sometimes (10-50% of the time); often (51-90% of the time); and routinely (>90% of the time) was used for questions of which a frequency of a particular action was inquired (e.g. how often a clinician would recommend an intervention). A pilot survey was performed by 5 non-critical care pharmacists to establish face and content validity of the survey instrument. Six critical care pharmacists not involved on the study team took the survey to estimate time required for completion and provide any additional feedback or areas for clarification. Verbal and written feedback from all pilot tests were incorporated into the final survey by the research team. The survey required approximately 10-15 minutes for completion.

2.2.2 Cross-Sectional Survey

Invitations to complete the survey were sent over e-mail twice, two weeks apart during April of 2017. The survey was administered through and data collected using

REDCap electronic data capture tools hosted at the University of Kentucky.[63] Invitations were sent out electronically via SCCM staff to all SCCM members of the CPP section, which includes pharmacist and non-pharmacist members. Pharmacist members of CPP practicing in adult critical care settings were specifically invited to take the survey and represent the target population of interest. Non-pharmacist members, or pharmacists practicing in a pediatric critical care setting, were asked not to respond to the survey.

2.2.3 Statistical Analysis

Data were analyzed with Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Categorical data from the survey are presented as proportions. Exploratory logistic regression analyses were undertaken to evaluate factors associated with the following: selection of often or routinely (e.g. >50% of the time) for loading doses for all six clinical scenarios examined, use of area-under-the-curve (AUC) as pharmacokinetic target parameter, and self-reported comfort with AUC calculations (i.e. somewhat or extremely comfortable). Candidate predictor variables identified *a priori* by the study team thought to influence vancomycin dosing practices included: region, practitioner years of experience, hospital type, hospital size, and ICU type. Due to complete separation of variables in some of the regression models, a penalized maximum likelihood regression model was used with the *firthlogit* package in Stata.[64-66] Output from regression models are presented as odds ratios (OR) with 95% confidence intervals (CI). Two-sided p-value <0.05 was considered statistically significant.

2.3 Results

2.3.1 Survey Response Rate

The survey was delivered to 2,305 SCCM CPP members (includes pharmacists and non-pharmacists) via e-mail using the SCCM CPP section distribution list. Approximately 1,500 of these members are pharmacists within the CPP section per the SCCM demographic database. Based on internal demographic data from the section indicating that approximately 100 pharmacists practiced in pediatric critical care, we estimate that 1,400 of these pharmacists practiced in an adult ICU setting and would be eligible for the survey. We received 364 responses, for an estimated response rate of 26%.

2.3.2 Respondent Demographics

Respondent demographics are presented in **Table 2.1**. Approximately half (48%) of respondents were from urban academic medical centers. The two most frequent responses for institutional bed size were 250-499 beds and 500-750 beds. The large majority of respondents (>97%) were from the United States with relatively similar representation from all major geographic areas. A majority of pharmacists participating in the survey were clinical practitioners < 5 years (33%) or 5-10 years (29%) removed from their terminal training. These pharmacists most frequently practiced in a medical (30%) or mixed medical/surgical (32%) ICU. Over 90% of pharmacist respondents reported that a pharmacist rounded with the primary or intensivist team at least five days per week.

2.3.3 Vancomycin-Related Practices in Respondent Institutions

Practice site characteristics regarding vancomycin are presented in **Table 2.2**. The most common responses regarding what percentage of *Staphylococcus aureus* isolates were methicillin-resistant *Staphylococcus aureus* (MRSA) were either 20-39% (23% of respondents) or 40-59% (34% of respondents). Vancomycin was routinely reported as empiric therapy in hospital-acquired infections by 67% of respondents. Fifty-five percent of respondents estimated the average duration of vancomycin use prior to de-escalation when MRSA is not cultured as 48-72 hours. A large majority of respondents (85%) reported that their institution reports the vancomycin minimum inhibitory concentrations for MRSA in the medical record.

Approximately one-third of respondents (31%) reported their institution had no formal pharmacy consult order (or pharmacy to dose protocol) to dose vancomycin. Another 31% of respondents reported that pharmacists may deviate from the protocol as written, which they sometimes do (10-50% of the time). The majority of pharmacists had a protocol or other mechanism in place to order vancomycin serum concentrations (83%), laboratory monitoring (e.g., such as a basic metabolic panel) (72%), or dose adjust according to vancomycin serum concentration or renal function (78%); 18% of respondents reported no formal mechanism for placing these orders, requiring they be placed under a provider's name pursuant to a verbal or written order.

Twenty percent of respondents reported a protocol for vancomycin dosing in the setting of CRRT with a mechanism to alert the pharmacist that CRRT is being initiated or discontinued; another 30% have a protocol with no mechanism to alert the pharmacist of

CRRT initiation or discontinuation. Most respondents (60%) did not use sustained low efficiency dialysis (SLED) at their practice site.

When asked which vancomycin monitoring and quality assurance programs were offered at their institutions, respondents indicated low rates of participation with regard to quality assurance for percentage of vancomycin dosing within a goal parameter (26%), clinical decision support to identify acute changes in serum creatinine or urine output (25%), and standardized definition of vancomycin-associated nephrotoxicity (7%).

2.3.4 Respondent Vancomycin Dosing Practices

Complete results are displayed in **Table 2.3**. With respect to scenario-based questions regarding use of vancomycin loading doses, responses were mixed across scenarios. The percentage of pharmacists reporting either routinely or often (51-90% of the time) using a loading dose for the surveyed conditions were as follows: meningitis/CNS infection (84%), septic shock (79%), infective endocarditis (75%), pneumonia in a mechanically ventilated patient (69%), sepsis without shock (61%), and pneumonia in a non-mechanically ventilated patient (54%). When respondents were asked why they did not administer a loading dose at times for a critically ill patient, the most common response was that their assessment of the patient did not meet the definition of severely ill (40%), followed by lack of clinical outcome data supporting the loading dose strategy (23%) and nephrotoxicity concerns (20%). Written comments by survey respondents suggested other possible reasons, including physician concerns for nephrotoxicity and logistics of having to compound the loading dose in the pharmacy

versus using doses readily available in the patient care area from automated dispensing cabinets.

Over 90% of respondents reported using actual body weight for loading doses and maintenance doses in normal or underweight patients. For overweight or obese patients, 56% of respondents reported using actual body weight (41% used adjusted body weight) for a loading dose and 45% of respondents reported using actual body weight (51% used adjusted body weight) for maintenance dosing. The most commonly reported dose cap for a loading dose was 2,000 mg (45%) followed by 2,500 mg (28%), while 2,000 mg was the most commonly reported dose cap for maintenance dosing with the majority of respondents (75%).

The majority of respondents reported rarely assessing post-loading dose concentrations, two level kinetics following the first dose, and peak levels. The vast majority (87%) of respondents reported using trough values while 13% reported using trough and AUC. When using trough values, 24% of respondents report that doses are held routinely pending evaluation of the level, while 64% report doses are held pending evaluation only in the setting of suspected acute kidney injury.

Pharmacists most commonly (92%) reported administering vancomycin via intermittent infusion with the majority of pharmacists rarely using continuous infusion. Pharmacist perception of their comfort level with AUC calculations was variable with intermittent infusion. The majority of respondents (62%) report being not at all comfortable with AUC calculations for continuous infusions.

In exploratory regression models, respondents from larger hospitals were overall less likely than smaller hospitals to report consistently using loading doses often or routinely in all six scenarios presented: 250-499 beds (OR 0.4, 95% CI 0.2-0.9), 500-750 beds (OR 0.4, 95% CI 0.2-0.9), and > 750 beds (OR 0.4, 95% CI 0.2-0.8) [reference hospitals with < 250 beds]. Europe (OR 22.8, 95% CI 2.3-228.7) and Western US regions (OR 3.6, 95% CI 1.5-8.6) were more likely to report using AUC as a target pharmacokinetic parameter for vancomycin use. No predictors were identified for reported comfort with AUC calculations.

2.4 Discussion

Compliance with clinical practice guidelines is influenced by many factors, notably the quality of the guidelines themselves, users of the guidelines, and implementation context.[67] Critical care pharmacists were overall compliant with many of the 2009 guideline recommendations assessed except for a few particular areas. Specifically, we observed inconsistent use of a loading dose, dosing weight in obese patients, and quality improvement efforts related to systematically monitoring vancomycin-associated nephrotoxicity.

A survey of infectious disease pharmacist self-reported adherence to the 2009 guidelines was previously published in 2013.[39] Key variations in infectious disease pharmacist reported practices from 2009 guideline recommendations involved the recommendations around loading doses in seriously ill patients (only 42% reported always), use of actual body weight to dose obese patients (40% reported sometimes; 52% reported always), and systematically monitoring nephrotoxicity with a standard definition

to routinely identify and report vancomycin-associated nephrotoxicity (34% reported never; 35% reported sometimes).[39] The authors of this study noted it imperative to discern reasons for noncompliance to the loading dose recommendation, particularly in severely ill patients who may benefit and have altered pharmacokinetics.[39] Our survey builds on prior work with a larger and more diverse study sample and is unique by focusing on adult critical care pharmacists, includes survey items regarding sources of practice variation related to vancomycin in critically ill patients, and investigates reasons for pharmacists not adhering to certain 2009 guideline recommendations.

Our survey also identified variation in compliance with loading dose recommendations; however, some pharmacists report practicing differently in specific scenarios. In particular, their assessment of severity of illness appears to be a large factor in administering a loading dose. Although some respondents may consider an ICU patient "severely ill" as the 2009 guidelines term it, this classification can be subjective.[38] Lack of clinical outcomes behind the 2009 recommendation for loading doses (IIIB recommendation) and concerns of nephrotoxicity in an already at-risk patient population are also commonly reported reasons for selectively administering loading doses.[38] Concerns of nephrotoxicity with loading doses by physician colleagues were also noted in the written responses from pharmacist respondents in this survey and identified as potential barriers to routinely using loading doses.

There were similar discrepancies between using actual body weight for dosing in obese patients between the two surveys, with a number of pharmacists in the current survey reporting use of an adjusted body weight.[39] The pharmacokinetics of vancomycin are known to be an area of controversy in obese patients.[68] Due to the hydrophilicity of

vancomycin and the increase in adipose tissue associated with obesity, its volume of distribution is somewhat increased in obese patients. In addition, various dosing weights, including ideal body weight, total body weight, and adjusted body weight, have been evaluated in estimating clearance of vancomycin with conflicting results.[69] Given the complexity of critically ill, obese patients and a lack of strong evidence for how to optimally dose vancomycin in these patients, it is not surprising that our survey revealed such practice variation.

In both our survey and that of Davis et al,[39] there do seem to be opportunities related to standardized definitions of vancomycin-associated nephrotoxicity and quality improvement programs to track and monitor this complication. The possibility exists that this is done within the context of antimicrobial stewardship programs and surveyed ICU pharmacists may not be aware, but this was reported as similarly low in the survey of infectious diseases pharmacists.[39] Additionally, an opportunity may exist for more institutions to implement CRRT alert triggers for pharmacists to increase or decrease doses, as appropriate.

The majority of critical care pharmacists surveyed rarely employed continuous infusion dosing of vancomycin. Interestingly, recent evidence suggests that continuous infusions may be less nephrotoxic than intermittent infusions, particularly in critically ill patients.[56,70,71] Of paradoxical interest is that pharmacists were reportedly far less comfortable with AUC calculations for continuous infusions than with intermittent infusions, given the AUC calculations for continuous infusion are much simpler than for intermittent dosing. The varying comfort level with AUC calculations in this survey demonstrates the importance of educational efforts that will be needed to employ AUC-

guided dosing in ICU patients on a larger scale, as is recommended by the revised vancomycin consensus guidelines recently published in May of 2020.[23]

Our exploratory analysis found that respondents from larger hospitals were generally less likely to report consistent use of loading doses compared to respondents from hospitals with < 250 beds. While the exact reasoning for this is unknown, it could be due to a relatively smaller number of respondents from hospitals with < 250 beds (15.1% of respondents) or perhaps improved compliance with protocols and guideline recommendations in smaller hospitals from this survey. Additionally, our analysis suggests geographic variation in early adoption of AUC to guide vancomycin dosing, with greater adoption in Western United States and Europe at the time our survey was administered. Pharmacist education is clearly required for AUC dosing and monitoring given the reported comfort rates. Although the pharmacokinetic assumptions are fewer and calculations easier with continuous infusion, this may simply represent the unfamiliarity of critical care pharmacists surveyed with employing continuous infusions due to the low frequency of use identified.

Our study has important limitations to acknowledge. Only SCCM CPP members participated in the study; thus, reported behaviors from non-survey responders and non-SCCM CPP members may be different. This survey only inquired about self-reported actions regarding vancomycin and may not reflect actual actions from clinicians in their practice. Multiple respondents may have responded from the same institution, thus biasing some reported metrics. Our response rate of 26% limited the number of respondents that we were able to collect data from, however, our study is more than twice as large as the prior study of vancomycin dosing practices.[39] Although Europe was

identified as using AUC more than others in this survey, there were few respondents from Europe, which may only represent a few institutions and not be representative of European practice. Finally, our survey was disseminated in the spring of 2017, and we suspect additional centers have transitioned to AUC monitoring at this time given a signal of increased safety in terms of kidney injury as well as anticipated (and actual) endorsement of AUC guided dosing in recently released revised consensus vancomycin guidelines.[23,36,72] Although these revised guidelines have been published since our survey, aside from recommending a change from trough-based dosing to AUC and no longer directly recommending actual body weight in maintenance dosing for obesity, many of the recommendations as they relate to our survey remain similar between the 2009 and 2020 guidelines.[23,38] **Table 2.4** compares relevant dosing considerations from our survey between the 2009 and 2020 guidelines.[23,38] Our data may serve as a benchmark in evaluating uptake of consensus guideline recommendations, particularly against the backdrop of showing a relatively low 'early-adopter' rate for AUC-guided dosing. In the context of newly revised consensus guidelines, we also show continued room for improvement with the guideline recommendation for loading doses, and demonstrate that a small percentage of surveyed pharmacists are employing continuous infusion. Finally, our survey also establishes the prevalence of important dosing concepts that may not be presented as formal guideline recommendations yet may reflect best practices in dosing vancomycin in critically ill patients, including electronic alerts for CRRT initiation or discontinuation.

2.5 Conclusion

Critical care pharmacists' reported practices regarding vancomycin are largely consistent with the 2009 vancomycin guideline recommendations. Important areas of variation include use of loading doses, dosing weights in obese patients, and quality improvement efforts related to systematically monitoring vancomycin-associated nephrotoxicity. Further study in these particular areas may allow more definitive guideline recommendations to help optimize vancomycin use in the critically ill.

Table 2.1 Respondent Demographics

	Number (%)
Practice Region	
Midwestern United States	111/364 (30.5)
Southern United States	109/364 (30.0)
Western United States	74/364 (20.3)
Northeastern United States	60/364 (16.5)
Outside of United States	10/364 (2.7)
Institutional Setting	
Academic medical center/urban	174/364 (47.8)
Community hospital/teaching/urban	89/364 (24.5)
Community hospital/non-teaching/urban	44/364 (12.1)
Other (including government and rural hospitals)	57/364 (15.6)
Institution Size	
< 250 beds	55/364 (15.1)
250-499 beds	119/364 (32.7)
500-750 beds	99/364 (27.2)
> 750 beds	91/364 (25.0)
Current Level of Training	
Current PGY2 specialty pharmacy resident (any specialty)	35/364 (9.6)
Practitioner less than 5 years out from terminal training	121/364 (33.2)
Practitioner 5-10 years out from terminal training	104/364 (28.6)
Practitioner more than 10 years out from terminal training	99/364 (27.2)
Other	5/364 (1.4)
Primary Location or Service	
Cardiothoracic ICU	20/364 (5.5)
Emergency Department	20/364 (5.5)
Medical ICU	109/364 (29.9)
Mixed Medical/Surgical ICU	115/364 (31.6)
Surgical/Trauma ICU	49/364 (13.5)
Other	51/364 (14.0)
Pharmacists Physically Round with the Primary or Intensivist Team ≥ 5 days/Week	
Yes	332/364 (91.2)

Table 2.2 Practice Site Characteristics and Vancomycin-Related Demographics

	Number (%)
Institutional Protocol Description and Pharmacist Adherence	
Pharmacists must adhere to the protocol as written and may not deviate	8/364 (2.2)
Pharmacists may deviate from the protocol as written, but I rarely[a] do	36/364 (9.9)
Pharmacists may deviate from the protocol as written, which I sometimes[b] do	111/364 (30.5)
Pharmacists may deviate from the protocol as written, which I often[c] do	63/364 (17.3)
Pharmacists may deviate from the protocol as written, and I routinely[d] do	34/364 (9.3)
No formal protocol exists in my primary practice	112/364 (30.8)
Pharmacist Authorized to Order	
Vancomycin levels	303/364 (83.2)
Laboratory tests for monitoring (e.g., basic metabolic panel)	262/364 (72.0)
Dose adjustments based on vancomycin levels or renal function changes	283/364 (77.8)
Institutional Protocol for Vancomycin Dosing in Continuous Renal Replacement Therapy (CRRT)	
Yes; but there is no mechanism to alert the pharmacist that CRRT is being initiated or discontinued	109/364 (29.9)
Yes; and there is a mechanism to alert the pharmacist that CRRT is being initiated or discontinued	71/364 (19.5)
No; and there is no mechanism to alert the pharmacist that CRRT is being initiated or discontinued	93/364 (25.6)
No; but there is a mechanism to alert the pharmacist that CRRT is being initiated or discontinued	51/364 (14.0)
Primary practice ICU does not utilize CRRT	40/364 (11.0)
Institutional Vancomycin Monitoring and Quality Assurance Programs	
Quality assurance for percentage of vancomycin dosing regimens within goal target parameters	96/364 (26.4)
Real-time clinical decision support to notify pharmacists of acute changes in serum creatinine or urine output	90/364 (24.7)
Standardized definition of vancomycin-associated nephrotoxicity	27/364 (7.4)
None of these	159 (43.7)
Estimated Methicillin Resistant *Staphylococcus aureus* Isolates	
20-39%	84/364 (23.1)
40-59%	122/364 (33.5)
60-80%	25/364 (6.9)
Other	32/364 (8.8)
Unknown/No specific antibiogram	101/364 (27.7)
Estimated Frequency of Empiric Vancomycin Therapy for Suspected Hospital-Acquired Infections	
Rarely[a]	6/364 (1.6)
Sometimes[b]	16/364 (4.4)
Often[c]	99/364 (27.2)
Routinely[d]	243/364 (66.8)
Estimated Average Duration of Vancomycin Use Prior to De-escalation when MRSA is Not Cultured	
< 2 days (< 48 hours)	16/364 (4.4)
2-3 days (48-72 hours)	201/364 (55.2)
3-4 days (72-96 hours)	109/364 (30.0)
> 4 days (> 96 hours)	38/364 (10.4)

[a] = < 10% of the time; [b] = 10-50% of the time; [c] = 51-90% of the time; [d] = > 90% of the time

Table 2.3 Vancomycin Dosing and Monitoring Strategies

Frequency of Loading Dose Recommendation By Indication				
	Rarely[a]	**Sometimes**[b]	**Often**[c]	**Routinely**[d]
Infective endocarditis	52/364 (14.3)	40/364 (11.0)	70/364 (19.2)	202/364 (55.5)
Meningitis/CNS infection	33/364 (9.1)	27/364 (7.4)	54/364 (14.8)	250/364 (68.7)
Pneumonia in a MV patient	51/363 (14.1)	60/363 (16.5)	75/363 (20.7)	177/363 (48.8)
Pneumonia in a non-MV patient	94/363 (25.9)	74/363 (20.4)	71/363 (19.6)	124/363 (34.2)
Sepsis with shock	40/364 (11.0)	38/364 (10.4)	68/364 (18.7)	218/364 (59.9)
Sepsis without shock	67/363 (18.5)	74/363 (20.4)	82/363 (22.6)	140/363 (38.6)
Pharmacist Reasoning When Choosing Not to Administer a Loading Dose				
Lack of clinical outcome data supporting strategy				83/364 (22.8)
Nephrotoxicity concerns				73/364 (20.1)
Time required to infuse				13/364 (3.6)
The patient does not meet my definition of severely ill				146/364 (40.1)
Other				71/364 (19.5)
Most Commonly Used Weight for Dosing Vancomycin				
	Actual Body Weight	**Ideal Body Weight**	**Adjusted Body Weight**	
Loading dose for normal/underweight patients	353/361 (97.8)	5/361 (1.4)	3/361 (0.8)	
Loading dose for overweight/obese patients	201/361 (55.7)	12/361 (3.3)	148/361 (41.0)	
Maintenance dose for normal/underweight patients	341/361 (94.5)	9/361 (2.5)	11/361 (3.1)	
Maintenance dose for overweight/obese patients	162/361 (44.9)	16/361 (4.4)	183/361 (50.7)	
Most Commonly Used Dose Cap				
	2000 mg per dose	**2500 mg per dose**	**3000 mg per dose**	**>3000 mg per dose**	**No cap/max dose**
Loading dose	164/362 (45.3)	102/362 (28.2)	61/362 (16.9)	8/362 (2.2)	27/362 (7.5)
Maintenance dose	273/362 (75.4)	43/362 (11.9)	10/362 (2.8)	2/362 (0.6)	34/362 (9.4)
Use of the Following Strategies to Assess Vancomycin Exposure and Calculate Further Dosing				
	Rarely[a]	**Sometimes**[b]	**Often**[c]	**Routinely**[d]
Collect a post-loading dose level	322/361 (89.2)	29/361 (8.0)	3/361 (0.8)	7/361 (1.9)
Two-level kinetics after first dose	277/361 (76.7)	63/361 (17.5)	14/361 (3.9)	7/361 (1.9)
Collect peak levels	325/361 (90.0)	21/361 (5.8)	6/361 (1.7)	9/361 (2.5)
Collect trough levels	9/362 (2.5)	18/362 (5.0)	32/362 (8.8)	303/362 (83.7)
Frequency of Doses Held Pending Level Evaluation When Trough Levels are Collected				
Doses are held routinely (>90% of the time) pending level evaluation				87/362 (24.0)
Doses are held pending level evaluation only if kidney injury is suspected or known				233/362 (64.4)
Doses are held rarely (< 10% of the time), even if kidney injury is suspected or known				42/362 (11.6)

Table 2.3 (continued)

Target Pharmacokinetic Dosing and Monitoring Parameter				
Trough				314/363 (86.5)
AUC				2/363 (0.6)
Trough and AUC				47/363 (12.9)
Frequency of Vancomycin Dosing via Method of Administration				
	Rarely[a]	**Sometimes**[b]	**Often**[c]	**Routinely**[d]
Intermittent infusion	10/364 (2.8)	11/364 (3.0)	8/364 (2.2)	335/364 (92.0)
Continuous infusion	342/363 (94.2)	16/363 (4.4)	3/363 (0.8)	2/363 (0.6)
Comfort Level Assessing Vancomycin Levels to Calculate AUC				
	Not at all comfortable	**Somewhat Uncomfortable**	**Somewhat Comfortable**	**Extremely Comfortable**
Intermittent infusion	134/363 (36.9)	54/363 (14.9)	100/363 (27.6)	75/363 (20.7)
Continuous infusion	223/362 (61.6)	59/362 (16.3)	49/362 (13.5)	31/362 (8.6)

[a] = < 10% of the time; [b] = 10-50% of the time; [c] = 51-90% of the time; [d] = > 90% of the time; AUC= area-under-the-curve; CNS=central nervous system; MV= mechanically ventilated

Table 2.4 Comparisons Between 2009 and 2020 Vancomycin Consensus Guidelines Relevant to Survey of Dosing Practices

Dosing Consideration	**2009 Vancomycin Guidelines[38]**	**2020 Revised Consensus Guidelines[23]**
Monitoring Parameters	"Trough serum vancomycin concentrations are the most accurate and practical method for monitoring vancomycin effectiveness." (IIB)	"Trough-only monitoring, with a target of 15-20 mg/L, is no longer recommended based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA" (A-II) "In patients with suspected or definitive serious MRSA infections, an individualized target of the AUC/MIC ratio of 400 to 600 (assuming a vancomycin MIC of 1 mg/L) should be advocated to achieve clinical efficacy while improving patient safety." (A-II)
Loading Dose and Weight	**"**In seriously ill patients, a loading dose of 25-30 mg/kg (based on actual body weight) can be used to facilitate rapid attainment of target trough serum vancomycin concentration." (IIIB)	"In order to achieve rapid attainment of targeted concentrations in critically ill patients with suspected or documented serious MRSA infections, a loading dose of 20 to 35 mg/kg can be considered for intermittent-infusion administration of vancomycin." (B-II) "Loading doses should be based on actual body weight and not exceed 3,000 mg. More intensive and early therapeutic drug monitoring should also be performed in obese patients." (B-II)

Table 2.4 (continued)

Maintenance Dosing Weight	**“**Vancomycin dosages should be calculated on actual body weight. For obese patients, initial dosing can be based on actual body weight and then adjusted based on serum vancomycin concentrations to achieve therapeutic levels.” (IIA)	“Initial maintenance doses of vancomycin can be computed using a population pharmacokinetic estimate of vancomycin clearance and the target AUC in obese patients. Empiric maintenance doses for most obese patients usually do not exceed 4,500 mg/day, depending on their renal function.” (B-II)
Continuous Infusion	“Continuous infusion regimens are unlikely to substantially improve patient outcome when compared with intermittent dosing.” (IIA)	“The pharmacokinetics of continuous infusion suggest that such regimens may be a reasonable alternative to conventional intermittent-infusion dosing when the AUC target cannot be achieved.” (B-II)

CHAPTER 3 EFFICACY AND SAFETY OF VANCOMYCIN LOADING DOSES

Flannery AH, Wallace KW, Rhudy CN, Olmsted AS, Minrath RC, Pope SM, Cook AM, Burgess DS, Morris PE. Efficacy and Safety of Vancomycin Loading Doses in Critically Ill Patients with Methicillin-Resistant Staphylococcus aureus (MRSA) Infection. *Ther Adv Infect Dis*. 2021 [online ahead of print] https://doi.org/10.1177/20499361211005965

3.1 Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant pathogen in critically ill patients. In a nationwide surveillance study of United States hospitals, *Staphylococcus aureus* was responsible for 20% of nosocomial bloodstream infections, with an alarming increase in MRSA isolates more than doubling from 22% to 57% over the period from 1995-2001.[8] In critically ill patients, MRSA bacteremia is associated with a 22.1% higher attributable mortality rate compared to methicillin-sensitive *Staphylococcus aureus* (MSSA).[9] *S. aureus* is isolated in approximately one out of every five cases of ventilator-associated pneumonia, with approximately 56% MRSA isolates.[10]

Recent data suggest that inadequate attainment of a therapeutic vancomycin area-under-the-curve (AUC) to minimum inhibitory concentration (MIC) ratio on days 1 and 2 of therapy in MRSA bacteremia is associated with treatment failure.[73] Critically ill patients commonly receive significant fluid resuscitation and experience fluid shifts from the intravascular to the extravascular compartment, which increases the volume of distribution (V_d) for hydrophilic drugs such as vancomycin.[24,74] Accordingly, recently updated consensus guidelines on vancomycin state that a loading dose of 20-35 mg/kg actual body weight (not to exceed 3,000 mg) can be considered for critically ill patients with suspected or confirmed MRSA infection in order to ensure rapid attainment of appropriate serum concentrations.[23] However, this recommendation is limited by moderate strength of recommendation (B) and quality of evidence (II), and is primarily based on pharmacokinetic outcomes rather than a documented clinical benefit.[23]

In a recent survey of practitioners regarding vancomycin dosing in critically ill patients assessing self-reported consensus guideline compliance, use of loading doses for

a variety of clinical scenarios was highly variable, with respondents often citing the lack of evidence for the clinical decision to forego a loading dose, followed by concerns of nephrotoxicity.[75] Given that critically ill patients are particularly vulnerable to poor outcomes from MRSA infection and exhibit altered pharmacokinetics of vancomycin that may place them at risk of missing identified pharmacokinetic-pharmacodynamic targets, they are logically the population to gain the most benefit from loading doses of vancomycin. As such, we sought to determine if critically ill patients with MRSA infection demonstrated improved clinical outcomes when receiving vancomycin loading doses (versus not) in order to provide needed clinical data to augment the pharmacokinetic outcomes previously assessed in studies of vancomycin loading doses.

3.2 Material and Methods

3.2.1 Study Design

This was a single center, retrospective cohort study of critically ill patients admitted to any intensive care unit (ICU) from January 2008 to October 2016 within a 865-bed tertiary academic medical center that serves as a referral center for the state and surrounding regions. Patients were included in the study if they had a positive respiratory or blood culture for MRSA and had vancomycin initiated for MRSA during or up to 48 hours before an ICU admission. Exclusion criteria were as follows: weight ≥ 125 kg, any MRSA culture other than from blood or respiratory source, <1,000 colony forming units/ml or 1-2% MRSA on respiratory cultures, loading dose information missing (i.e. from outside hospital), or if vancomycin was started > 48 hours prior to the ICU admission. We elected to study pneumonia and bacteremia given the frequency of these infections in critically ill patients and their relative degree of morbidity compared to other

infections (i.e. skin and soft tissue) in an attempt to prognostically enrich the study for patients that might clinically benefit from a loading dose of vancomycin.[76] A weight of ≥ 125 kg was excluded so as not to confound the assessment of loading doses on a milligram per kg of actual body weight basis. Patients were classified into two cohorts based on their initial vancomycin dose received: loading dose (≥ 20 mg/kg actual body weight) or no loading dose (<20 mg/kg actual body weight).

The primary outcome was clinical failure, defined as a composite outcome with similar definitions as prior studies of MRSA infection,[77,78] which included: death within 30 days of first MRSA culture, blood cultures positive ≥ 7 days, white blood cell (WBC) count >12 $x10^3$ /mm^3 up to 5 days from vancomycin initiation, temperature >100.4°F up to 5 days from vancomycin initiation, or substitution (or addition) of another targeted anti-MRSA antibiotic such as daptomycin, linezolid, or ceftaroline. The primary outcome was adjudicated in the order of the outcomes stated above, thus while some patients may have had more than one definition of clinical failure, each patient was only classified with one of the definitions based on the sequential order assessed.

Secondary outcomes included all-cause mortality in the ICU, time from vancomycin initiation to ICU discharge, acute kidney injury (AKI) within 5 days of vancomycin initiation as assessed by the serum creatinine component of the Kidney Disease Improving Global Outcomes (KDIGO) criteria,[79] first vancomycin serum trough concentration value, and duration of vasopressor support, if applicable. Data were extracted from the electronic data warehouse and manual chart review was performed on all included patients to ensure integrity of the data. Data were collected on patients to ensure comparability at baseline, including potential factors hypothesized by the

investigators as being associated with receipt of a loading dose including severity of illness assessments such as Sequential Organ Failure Assessment score (SOFA)[80] and Pitt bacteremia score (PBS),[81,82] need for mechanical ventilation or vasopressor support at the time of vancomycin initiation, hospital service (classified into medical or surgical ICUs), history of kidney disease, and kidney function at the time of vancomycin initiation. Vancomycin MICs were determined per Clinical and Laboratory Standards Institute standards by broth microdilution via automated susceptibility testing methods with the Phoenix™ Automated Microbiology System (BD Diagnostics, Sparks, MD, USA) from 1/2008 to 10/2013 and 4/2016 to 10/2016 and Etest (bioMérieux, Marcy l'Etoile, France) from 11/2013 to 3/2016. Receipt of concurrent nephrotoxins within 5 days of receiving the loading dose was classified as the receipt of any of the following: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, intravenous (IV) acyclovir, aminoglycosides, amphotericin B, colistin, foscarnet, non-steroidal anti-inflammatory drugs, polymyxin B, sulfamethoxazole/trimethoprim, IV tacrolimus, and piperacillin/tazobactam. The study was approved by the institutional review board at the University of Kentucky (#54961) with a waiver of informed consent given the study design.

3.2.2 Statistical Analysis

Based on prior studies of MRSA infections suggesting clinical failure rates as high as 41%,[77,78] and assuming a higher percentage due to the requirement for critical illness in our study, we anticipated a baseline clinical failure of 60%. In order to detect a 20% decrease in the clinical failure, we determined 97 patients were required in each

group (194 patients in total) to achieve 80% power with an $\alpha = 0.05$ for the primary composite outcome.

Descriptive statistics were used to summarize categorical variables as percentages and continuous variables as medians (interquartile range [IQR]). Independent samples were compared using the chi-square test or Wilcoxon rank-sum test as appropriate. Given the relatively high frequency of death anticipated from studying critically ill patients, we analyzed time to ICU discharge from vancomycin initiation with a competing-risks regression approach using the methods of Fine and Gray[83] with death as a competing event and displayed graphically with a cumulative incidence function. Analysis of clinical failure by primary infection site (isolated bacteremia or pneumonia) between the loading dose and no loading dose groups was a pre-planned secondary analysis. Exploratory analyses of the primary outcome included the reconstruction of the loading dose variable in quartiles rather than a dichotomous variable, and evaluation of initial doses of ≥1,750 mg vs. <1,750 mg as hypothesized by other research groups to have benefit.[77] We built a multivariable logistic regression model for the composite outcome of clinical failure using the following pre-specified variables with complete data present identified by the study team with the potential to influence either the receipt of a loading dose or outcome of clinical failure at the time the vancomycin loading dose was administered: vancomycin initial dose (as a continuous mg/kg variable), age, sex, MRSA culture site, chronic or end-stage renal disease, ICU service, day 1 maximum values for WBC, blood urea nitrogen, serum creatinine, and temperature, SOFA score, need for vasopressor support, or need for mechanical ventilation. The PBS was not included due to presumed collinearity with SOFA and other variables included. Variance inflation

factors were used to assess collinearity and ensure all variables were appropriate to retain in the model. Statistical analyses were performed in Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) and SAS (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p< 0.05$.

3.3 Results

As shown in **Figure 3.1**, 871 patients were identified as having an ICU admission with a concurrent positive culture for MRSA during the specified ICU admission. Following application of the exclusion criteria, 449 patients were available for analysis. Of these patients, 103 (22.9%) received a loading dose while 346 (77.1%) did not. Patient demographics for the cohort are shown in **Table 3.1.** The cohort consisted primarily of patients on medical services with approximately half of MRSA cases isolated from respiratory cultures. Approximately 3/4th of the cohort required mechanical ventilation and 1/3rd required vasopressor support at the time of vancomycin initiation. Patients were well-matched in terms of baseline characteristics between the two groups. Patients in the loading dose group received higher initial doses on a mg (1500 [1250-1750] vs. 1250 [1000-1500]; $p<0.001$) and a mg/kg actual body weight basis (21 [20-22] vs. 16 [15-18]; $p<0.001$) compared to the no loading dose group. Patients classified as receiving a loading dose tended to weigh less than patients in the no loading dose group (68 [61-85] kg vs. 80 [66-97] kg; $p<0.001$). Only one patient received an initial vancomycin dose greater than 2 grams. All patients were administered vancomycin via intermittent infusion.

There was no difference in the percentage of patients experiencing clinical failure between the loading dose and no loading dose groups (74.8% vs. 72.8%; $p= 0.698$), with

no significant difference between groups in any component of the composite outcome (**Table 3.2**). No differences were noted between groups in any of the secondary outcomes, including all-cause ICU mortality, AKI, or duration of vasopressor or mechanical ventilatory support. The first serum vancomycin trough concentration was slightly higher in the loading dose group, but this did not reach statistical significance (15.6 [11.0-24.4] mcg/mL vs. 14.0 [9.5-21.0] mcg/mL; p=0.056). There were no differences in WBC or maximum temperature in days 2-5 following the initiation of vancomycin (**Table 3.3, Figure 3.2).** In a simple competing risk regression model with death as a competing event, use of a loading dose was not associated with time to ICU discharge from vancomycin initiation (Subdistribution hazard ratio 1.09; 95% confidence interval 0.86-1.40). The cumulative incidence function is shown in **Figure 3.3**. In the subgroup of patients with isolated MRSA bacteremia, there was no difference in clinical failure between the loading dose and no loading dose groups: 30/34 (88.2%) vs. 63/80 (78.8%); p=0.232. Similarly, in patients with MRSA respiratory cultures (with or without bacteremia), there were no differences between loading dose and no loading dose groups: 47/69 (68.1%) vs. 188/265 (70.9%); p=0.647.

In exploratory analyses of the primary outcome, the vancomycin dose (in mg/kg actual body weight) was assessed in quartiles rather than a dichotomous variable and there were no significant differences in the frequency of clinical failure (p=0.794; **Table 3.4**). Similarly, when initial doses of ≥ 1,750 mg were compared with doses <1,750 mg, there was no difference in clinical failure between the two groups (p=0.485; **Table 3.5**). In the adjusted multivariable logistic regression model, the first dose of vancomycin

(expressed in mg/kg as a continuous variable) was not associated with clinical failure: odds ratio (OR) 0.98 (95% confidence interval (CI) 0.91-1.06) (**Table 3.6**).

3.4 Discussion

This represents the first study to our knowledge to assess clinical outcomes associated with vancomycin loading doses recommended by consensus guidelines in critically ill patients with MRSA infection,[23] and the largest study of vancomycin loading doses in any patient population. While the ideal design to answer this clinical question is a randomized controlled trial, given the literature that every hour delay in antibiotics in a patient with sepsis is associated with a 7.6% reduction in survival,[40] including similar literature in *S. aureus* bacteremia specifically,[84] obtaining informed consent during this window for a definitively large study in critically ill patients is likely to hinder such a trial ever being done, particularly for confirmed MRSA infection rather than all patients receiving empiric vancomycin.

A randomized controlled trial of vancomycin loading doses in the emergency department showed that a loading dose of 30 mg/kg vs. 15 mg/kg resulted in higher trough values at 12- and 24- hours, but not by 36-hours, with no significant difference in AKI or clinical outcomes between the two groups.[85] Similarly, other observational studies have shown an association between loading doses and higher target attainment of initial trough values without increasing the risk of AKI,[86,87] although improved target trough attainment is not consistent across the literature.[78,88] Similar to other studies, we did not observe any increased risk of AKI with use of a vancomycin loading dose.[85,86] Particularly with updated consensus guidelines recommending AUC assessment at this juncture rather than trough assessment,[23] the existing literature linking vancomycin

loading doses to trough attainment as justification for use of a particular dosing strategy deserves reevaluation. Thus, there is an increasing importance to evaluate clinical outcomes regarding the decision to administer a loading dose.

One small cohort study found an association of vancomycin loading doses (≥ 20 mg/kg) with clinical response, as defined by survivors with a ≥ 30% reduction in WBC count or C-reactive protein, or decline in fever over 48-72 hours; however, the number of MRSA cases from the cohort studied was relatively small.[78] In a larger study of MRSA bacteremia, loading doses (≥ 20 mg/kg) were not associated with treatment failure; however, in a post-hoc analysis where loading doses were reclassified as ≥ 1,750 mg, a protective effect of loading doses was noted.[77] In both studies, loading doses were not associated with nephrotoxicity.[77,78] Of note, critically ill patients were not the focus of these prior studies, and ICU patients comprised approximately 25% of the cohort.[77] Our study did not find a benefit of loading doses on any of the distinct outcomes that we included in the primary composite outcome, nor when assessed by site of infection as a subgroup analysis. Similarly, there was no signal of benefit noted in the sensitivity analysis examining quartiles of loading doses, the reclassification of loading doses as 1,750 mg or higher, or in the multivariable logistic regression model evaluating initial dose on a mg/kg basis as a continuous variable.

As noted previously, a recent survey of vancomycin dosing practices in critically ill patients revealed that a lack of clinical outcome data, concerns of nephrotoxicity, and time delay of admixed custom doses from the pharmacy (in the case of a loading dose) vs. pre-mixed drug from automated dispending cabinet limited application of loading doses in all cases.[75] Our data suggest loading doses of vancomycin do not increase the

risk of AKI, even in critically ill patients with multiple risk factors for AKI. However, the data also suggest no clinical benefit of loading doses even in confirmed MRSA infections in critically ill patients, thus supporting the noted clinician hesitation. Indeed, given the increase in mortality with every hour delay in antibiotic therapy,[40,84] our study supports the notion that therapy should not be delayed for dose customization to meet the specified loading dose criteria. This finding not only applies to emergency departments, post-anesthesia care units, and other ICU triage areas in resource-intensive healthcare settings, but may also be a relevant consideration to care provisions in lower resource-intensive settings where dose customization for loading doses may be limited. Although the mechanistic explanation of our findings is less clear for patients with bacteremia, the relatively poor ability of vancomycin to concentrate in pulmonary tissue, particularly after a single dose, may explain the lack of difference in clinical outcomes observed in our study.[89] Additionally, considering the literature associating a delay in second dose of antibiotics for patients admitted from the emergency department with sepsis with outcomes including mortality,[90] our study suggests that the initial, loading dose of vancomycin may not significantly influence clinical outcomes in critically ill patients, and a greater emphasis be placed on ensuring timely initiation of subsequent doses to ensure appropriate efforts to attain goal AUC:MIC targets for the initial 24 hour period.

Strengths of our study included the large sample size, which was sufficiently powered to determine differences in clinical failure. We built on previous literature by studying only confirmed cases of MRSA and expanding on the study of pharmacokinetic outcomes to clinical outcomes of this patient population. Our definition of clinical failure has been used in other studies of MRSA infection and all components are measured

objectively, thus not relying on subjective assessments such as clinical resolution.[77,78] Anticipating that detecting a difference in an outcome such as ICU length of stay or vasopressor duration would require several fold additional patients, the outcome of clinical failure is sensitive to surrogate outcomes such as WBC and temperature changes over time that may have seen more immediate effects from the loading dose, if present. The two groups of patients were similar in terms of severity of illness, kidney disease, and other pre-identified factors that might have predisposed to receipt of a loading dose or clinical outcome. We also included multiple types of infections commonly afflicting critically ill patients.

Our study also has noted limitations, including the retrospective, non-randomized, and single center design. Due to vancomycin dosing practices at the institution, we are not able to make any inferences about the clinical benefits of loading doses beyond 2,000 mg as only one patient received a > 2,000 mg loading dose. However, a dose cap of 2,000 mg was the most commonly reported dose cap in a prior study of vancomycin dosing practices among critical care pharmacists suggesting this practice is widespread.[75] Relevant to this study, any patient over 100 kg was therefore essentially ineligible to be categorized as having received a loading dose. Accordingly, whether or not relatively larger loading doses (up to 3,000 mg as maximally defined in current consensus guidelines)[23] are associated with any clinical benefit remains unknown at this time, although the lack of dose response noted in the exploratory analysis of loading dose by quartiles would suggest against this. Our study design also excluded patients weighing ≥ 125 kg, thus our results may not be directly applicable to obese patients. The difference in the initial vancomycin dose between the loading dose and no loading dose cohorts was

not as drastic as would have been the case if higher loading doses were used in our study. The loading dose group received an additional 5 mg/kg (or 250-500 mg typically). While dichotomization of information can have drawbacks, use of a loading dose or not is typically a dichotomous decision clinically. Additionally, the lack of signal in the quartile analysis and in the multivariable regression where initial dose was analyzed as a continuous variable supports the findings that initial dose does not appear to impact clinical failure. We also did not estimate or measure vancomycin AUC in these groups as a result of the loading dose, or in subsequent dosing intervals, and thus are unable to directly compare vancomycin AUC with these clinical outcomes. The known variability in vancomycin pharmacokinetics in critically ill patients makes it possible that patients in this study may have not achieved adequate AUC with the loading doses thus explaining the lack of clinical benefit observed. For example, a significant number of these patients may have had AKI upon admission or been actively fluid resuscitated at the time of vancomycin loading dose, which would have increased the V_d and may have influenced the ability to achieve the target exposure with the vancomycin doses observed in the study. More patients had respiratory infections than bacteremia, thus if there was a differential effect of loading doses given the site of infection, we may have been underpowered to detect it. Finally, although patients appeared to be well-matched based on identified characteristics, we cannot rule out residual confounding and its effects.

3.5 Conclusion

In critically ill patients with MRSA infection cultured from the blood or respiratory tract, receipt of a loading dose of vancomycin (≥ 20 mg/kg actual body

weight) was not associated with any differences in clinical failure, mortality, ICU length of stay, AKI, or other outcomes when compared to patients not receiving a loading dose.

Table 3.1 Baseline Demographics

Patient Demographic	**Loading Dose (n=103)**	**No Loading Dose (n=346)**	**p-value**
Age (years)	54 (38-66)	57 (45-68)	0.102
Sex (% male)	58 (56.3%)	198 (57.2%)	0.869
Culture Site			0.099
Blood	34 (33.0%)	80 (23.2%)	
Respiratory	55 (53.4%)	199 (57.7%)	
Both	14 (13.6%)	66 (19.1%)	
Chronic Kidney Disease (%)	8 (7.8%)	41 (11.9%)	0.243
End Stage Renal Disease (%)	7 (6.8%)	23 (6.7%)	0.958
Service (% medical)	80 (77.7%)	234 (67.6%)	0.051
Minimum inhibitory concentration (mcg/ml)[a]	1 (1-1)	1 (1-1)	0.352
Long Term Indication for MRSA Treatment[b]	12 (11.7%)	25 (7.2%)	0.216
Weight (kg)	68 (61-85)	80 (66-97)	<0.001
Initial vancomycin dose (mg)	1500 (1250-1750)	1250 (1000-1500)	<0.001
Initiation vancomycin dose (mg/kg actual body weight)	21 (20-22)	16 (15-18)	<0.001
Number of concurrent nephrotoxins within first 5 days	1 (0-2)	1 (1-2)	0.441
Vancomycin therapy duration (days)	6 (3-12)	6 (3-11)	0.843
At Time of Vancomycin Initiation			
White blood cell count ($x10^3/mm^3$)	15 (10-21)	13 (9-19)	0.150
Blood urea nitrogen (mg/dl)	23 (15-41)	26 (15-41)	0.625
Serum creatinine (mg/dl)	1.1 (0.7-1.6)	1.0 (0.7-1.7)	0.902
Maximum Temperature (°F)	100.4 (98.7-102.0)	100.7 (99.3-102.3)	0.101
Sequential Organ Failure Assessment score	8 (5-10)	7 (5-10)	0.674
Pitt Bacteremia Score	5 (4-7)	5 (3-7)	0.607
Requirement for vasopressor support (%)	31 (30.1%)	105 (30.4%)	0.961
Mechanical ventilation (%)	77 (74.8%)	254 (73.6%)	0.818
Lactate (mmol/L)[c]	1.8 (1.1-3.3)	1.6 (1.1-3)	0.586

[a]Available for 295 patients

[b]Long-term indication defined as ≥ 4 weeks of therapy

[c]Available for 366 patients

Table 3.2 Study Outcomes

Outcome	**Loading Dose (n=103)**	**No Loading Dose (n=346)**	**p-value**
Primary Outcome			
Clinical failure (%)	77 (74.8%)	252 (72.8%)	0.698
Death within 30 days (%)	20 (19.4%)	77 (22.3%)	--
Blood cultures positive ≥ 7 days (%)	12 (11.7%)	16 (4.6%)	--
WBC >12 x10^3 /mm^3 after 5 days	28 (27.2%)	93 (26.9%)	--
Persistent temperature >100.4° F after 5 days	8 (7.8%)	36 (10.4%)	--
Substitution/addition of alternative treatment	9 (8.7%)	30 (8.7%)	--
Secondary Outcomes			
All-cause mortality in ICU (%)	21 (20.4%)	87 (25.1%)	0.321
Time from vancomycin initiation to ICU discharge (days)	9.4 (4.4-16.7)	9.5 (4.9-17.4)	0.880
Acute kidney injury within 5 days of vancomycin initiation (%)[a]	20 (20.2%)	59 (17.8%)	0.765
Duration of vasopressor support (days)[b]	3 (2-5)	3 (2-6)	0.793
Duration of mechanical ventilation (days)[c]	8.5 (4.3-17)	9 (4-20)	0.632
First vancomycin serum trough concentration (mcg/ml)[d]	15.6 (11.0-24.4)	14.0 (9.5-21.0)	0.056

WBC = white blood cell count

[a]Patients with End Stage Renal Disease excluded from assessment

[b]Available for the 136 patients requiring vasopressor support at vancomycin initiation

[c]Available for the 331 patients requiring mechanical ventilation at vancomycin initiation

[d]Available for 361 patients

Table 3.3 White Blood Cell and Temperature Values Over Time

Value	**Loading Dose (n=103)**	**No Loading Dose (n=346)**	**p-value**
WBC (x10^3 /mm^3)			
Day 2	11.8 (8.9-17.3)	12.5 (8.9-18.7)	0.814
Day 3	10.8 (7.9-15.7)	11.9 (8.8-17.9)	0.254
Day 4	11.1 (7.9-15.8)	11.3 (7.7-16.5)	0.936
Day 5	10.7 (7.6-14)	11 (7.4-16.4)	0.446
Temperature (°F)			
Day 2	100.1 (99.0-101.1)	100.4 (99.1-101.4)	0.144
Day 3	100.0 (98.7-101.1)	99.8 (98.9-101.0)	0.680
Day 4	99.4 (98.6-100.4)	99.6 (98.8-100.7)	0.158
Day 5	99.3 (98.5-100.2)	99.5 (98.7-100.5)	0.155

Table 3.4 Primary Outcome Assessed by Quartiles of Initial Dose (mg/kg)

Initial Dose Quartile (mg/kg actual body weight)[a]	**No Clinical Failure (n=120)**	**Clinical Failure (n=329)**
1st quartile (7.9-15.1)	29 (25.7%)	84 (74.3%)
2nd quartile (15.1-17.2)	34 (30.4%)	78 (69.6%)
3rd quartile (17.2-19.3)	29 (25.9%)	83 (74.1%)
4th quartile (19.3-27.6)	28 (25.0%)	84 (75.0%)

[a]p=0.794

Table 3.5 Primary Outcome with Loading Dose Categorized as ≥ 1,750 mg

Outcome	**Loading Dose (n=100)**	**No Loading Dose (n=349)**	**p-value**
Clinical Failure (%)	76 (76.0%)	253 (72.5%)	0.485

Table 3.6 Multivariable Logistic Regression Model for Clinical Failure

Variable	**Odds Ratio with 95% Confidence Interval**	**p-value**
First vancomycin dose (mg/kg)	0.98 (0.91-1.06)	0.617
Age (years)	1.01 (0.99-1.02)	0.418
Sex (male vs. female)	0.73 (0.44-1.21)	0.226
Infection Site (compared to blood alone)		
Respiratory	0.41 (0.21-0.81)	0.011
Concomitant blood and respiratory	0.47 (0.21-1.08)	0.074
End stage renal disease	0.17 (0.05-0.56)	0.003
Chronic kidney disease	1.06 (0.45-2.46)	0.899
ICU service (surgical vs. medical)	1.20 (0.70-2.07)	0.503
Day 1 white blood cell count ($x10^3/mm^3$)	1.08 (1.04-1.12)	<0.001
Day 1 blood urea nitrogen (mg/dl)	0.98 (0.97-0.99)	0.016
Day 1 serum creatinine (mg/dl)	1.35 (1.04-1.76)	0.023
Day 1 maximum temperature (°F)	0.97 (0.85-1.10)	0.597
Sequential Organ Failure Assessment score	1.23 (1.09-1.37)	<0.001
Requirement for vasopressor support (%)	0.61 (0.31-1.21)	0.156
Mechanical ventilation (%)	0.77 (0.36-1.65)	0.500

Figure 3.1 Application of Inclusion and Exclusion Criteria

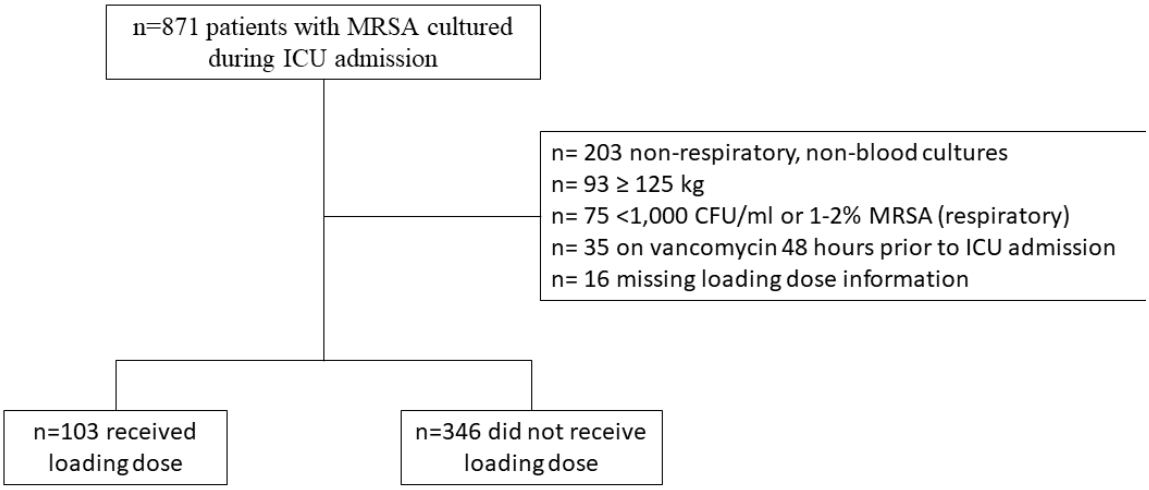
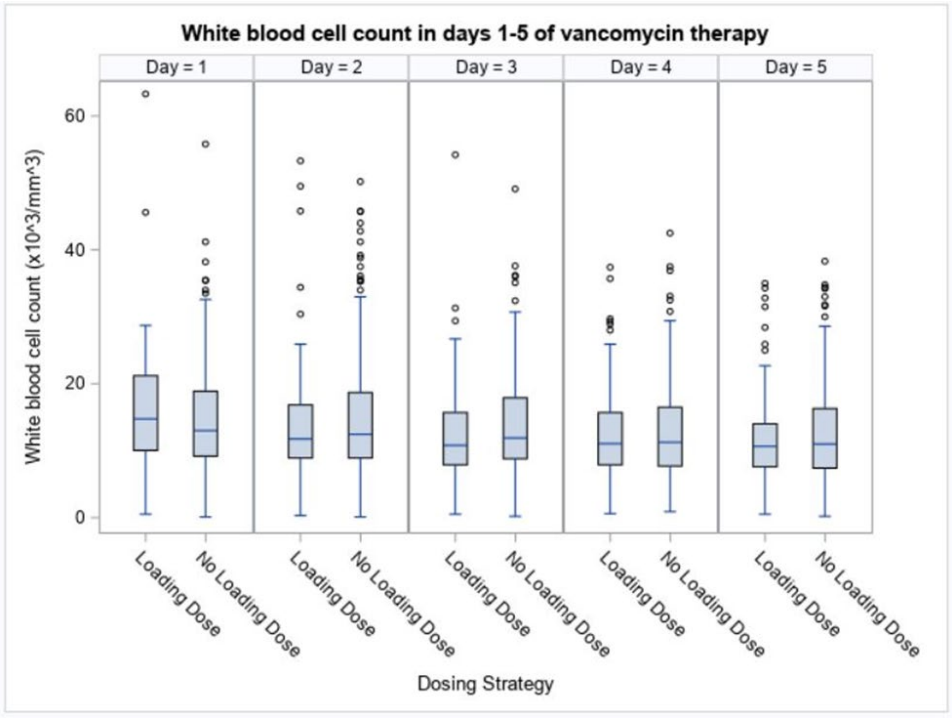


Figure 3.2 Daily White Blood Cell Count and Temperature Trends



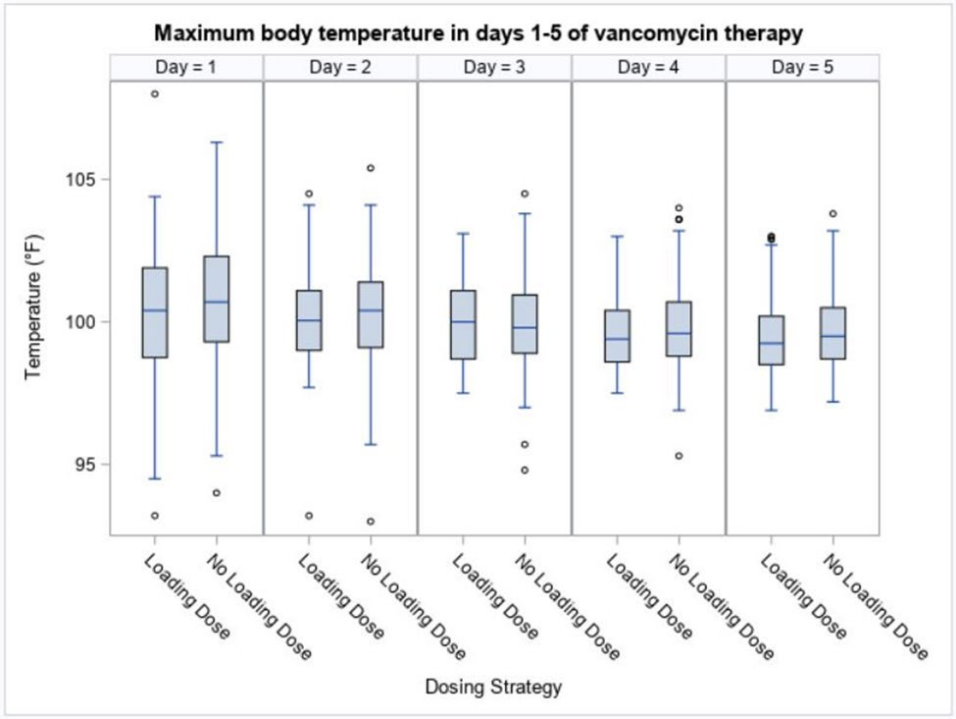
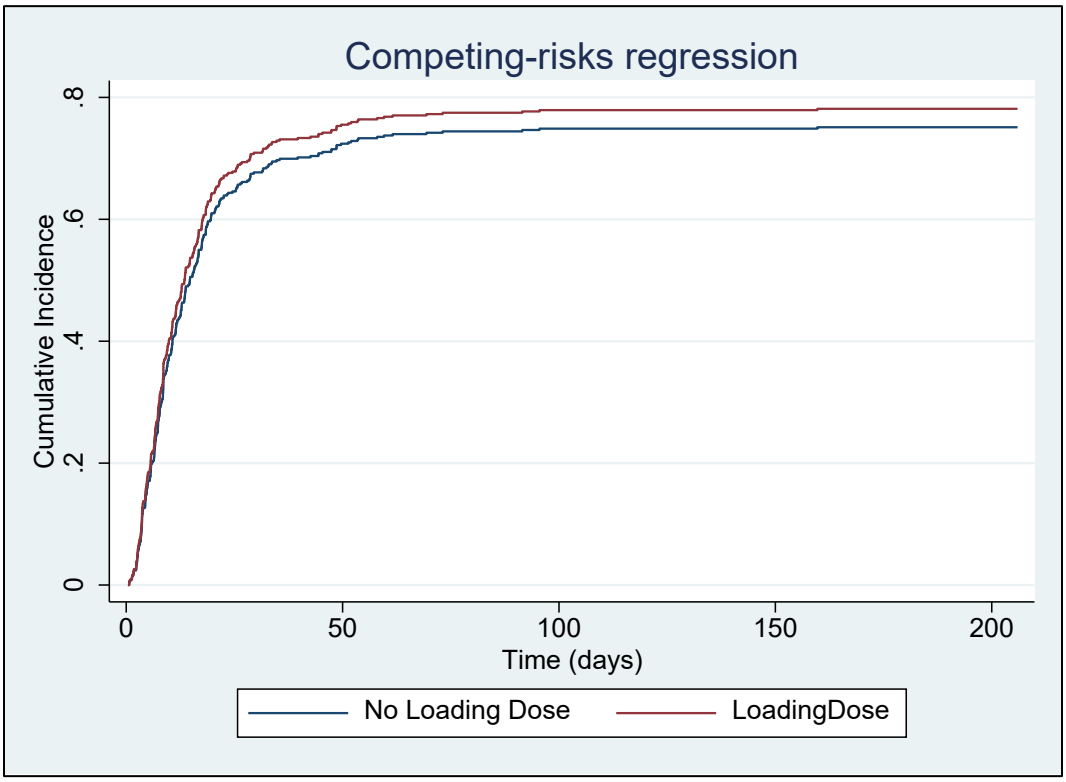


Figure 3.3 Cumulative Incidence Function for Time to ICU Discharge from Vancomycin Initiation



CHAPTER 4 FIRST-DOSE VANCOMYCIN PHARMACOKINETICS

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Flannery AH, Delozier NL, Effoe SA, Wallace KL, Cook AM, Burgess DS. First-Dose Vancomycin Pharmacokinetics Versus Empiric Dosing on Area-Under-the-Curve Target Attainment in Critically Ill Patients. *Pharmacotherapy*. 2020 Dec;40(12):1210-1218. doi: 10.1002/phar.2486.

4.1 Introduction

Revised consensus guidelines for therapeutic drug monitoring (TDM) of vancomycin recommend a shift from trough-based monitoring to area-under-the-curve (AUC) monitoring, with a daily goal (assuming a minimum inhibitory concentration (MIC) of 1 mg/L) of 400-600 mg·h/L.[23] Failure to obtain sufficient AUC/MIC target attainment early in therapy (days 1 and 2) has been associated with treatment failure in Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and endocarditis.[73,91] On the other hand, AUC values greater than 600-650 mg·h/L are associated with acute kidney injury (AKI).[37,92] Critically ill patients with infection are already susceptible to AKI and often show altered pharmacokinetic changes that can markedly impact vancomycin's volume of distribution (V_d) and clearance (CL).[93] Thus, approaches to optimize vancomycin AUC target attainment early in therapy for critically ill patients with confirmed or suspected MRSA infection are needed.

As an early adopter of AUC-guided vancomycin dosing, our center has several years of experience with AUC monitoring of vancomycin in a wide variety of patient populations.[94] We developed a protocol using serum vancomycin concentrations obtained following the first dose of vancomycin to calculate patient-specific pharmacokinetic parameters used for further dosing as one approach to target precision dosing of vancomycin in high-risk patients, including the critically ill. Alternatively, empiric dosing based on population pharmacokinetic estimates was also available as a method to develop initial vancomycin regimens targeted at AUC values. The use of first-dose kinetics to guide dosing and the subsequent impact on vancomycin trough attainment has demonstrated mixed results in prior studies.[42,43] The availability of both dosing

approaches allowed a unique opportunity to compare dosing strategies of vancomycin on AUC target attainment in critically ill adults.

We sought to test a personalized dosing strategy, using two concentrations following the initial dose of vancomycin and employing first-dose pharmacokinetic calculations to guide subsequent dosing, versus dosing with population pharmacokinetic estimates on the outcome of vancomycin AUC target attainment assessed at steady state (SS) in critically ill patients receiving vancomycin.

4.2 Methods

4.2.1 Study Design

The University of Kentucky Chandler Medical Center is an 865-bed tertiary care referral center for the state and surrounding region. For inpatients, all scheduled vancomycin therapy is dosed per pharmacist protocol approved by the Pharmacy and Therapeutics Committee. Pharmacists may alter vancomycin dosages, order vancomycin levels, and order laboratory tests for monitoring such as a basic metabolic panel for serum creatinine. In September of 2017, in anticipation of vancomycin TDM guideline changes, the monitoring of vancomycin was changed from trough-based to AUC as previously described.[94]

In a retrospective cohort design, all patients admitted to the medical intensive care unit (MICU) from September 2017 to June 2019 with at least two vancomycin serum concentrations ordered to calculate AUC at SS and receiving > 1 dose of intravenous vancomycin were assessed for inclusion in the study. Patients were excluded if serum concentrations were obtained following the first dose but no SS levels (therapy was discontinued before SS concentrations obtained), if receiving intermittent vancomycin

dosing due to AKI or the receipt of renal replacement therapy, if they received vancomycin at an outside hospital prior to transfer (as first-dose vancomycin concentrations would not have been able to be obtained), or if the vancomycin concentrations were drawn incorrectly (i.e. drawn from non-flushed catheter) or laboratory error was suspected by the assessing pharmacist as determined by documented records.

This resulted in a cohort of critically ill patients that received vancomycin with at least two SS levels obtained for AUC calculation. From this cohort, two groups were identified: those patients in whom vancomycin concentrations were obtained following the first dose to guide subsequent dosing (first-dose kinetics) and those patients dosed based on population estimates (empiric dosing). Accordingly, the first-dose kinetics group had four vancomycin concentrations drawn (two for first-dose pharmacokinetic calculation and two at SS for AUC calculation) and the empiric dosing group had two concentrations assessed (at SS for AUC calculation). The primary outcome was goal AUC target attainment (defined as 400-600 mg·h/L) at SS. Secondary outcomes included AKI between the first-dose kinetics and empiric dosing groups (assessed starting at the time SS levels were drawn and up to 48 hours following SS levels using the serum creatinine component of the Kidney Disease Improving Global Outcomes [KDIGO] criteria[79]) and a comparison of pharmacokinetic parameters (elimination rate constant (k_e), V_d, CL,) between the time of first dose and SS in the first-dose kinetics group. Pharmacokinetic parameters and creatinine clearance were also compared between the first-dose kinetics group and empiric dosing group at steady state to ensure comparability. Requisite data were collected on serum vancomycin concentrations,

vancomycin doses, infusion times, intervals, and time stamps necessary to confirm calculated AUC. Demographic data collected include patient age, sex, weight, height, serum creatinine, serum blood urea nitrogen, Sequential Organ Failure Assessment (SOFA) score[80], and receipt of concurrent nephrotoxins from initiation of vancomycin up to 48 hours following SS (defined as angiotensin converting enzyme inhibitors, acyclovir (intravenous), aminoglycosides, amphotericin B, angiotensin receptor blockers, colistin, foscarnet, nonsteroidal anti-inflammatory drugs, polymyxin B, sulfamethoxazole/trimethoprim, tacrolimus (intravenous), and piperacillin /tazobactam). Creatinine clearance (CrCl) was estimated with Cockcroft-Gault[95] or Salazar-Corcoran[96] if greater than 125% of ideal body weight. The electronic medical record was manually reviewed to obtain the necessary data and confirm accuracy of all calculations. The study was approved by the Institutional Review Board at the University of Kentucky.

4.2.2 Vancomycin Dosing Protocol

During the study period, two options existed for calculation of empiric vancomycin dosing for patients with stable renal function. One option allowed for assessing two serum vancomycin concentrations following the first dose and using first-dose pharmacokinetics to develop a personalized dosing regimen based on the patient's established pharmacokinetic parameters. This approach was primarily used in the MICU as opposed to other units in the hospital based on pharmacist preference. Alternatively, population estimates for V_d and k_e could be used to develop a regimen anticipated to produce a daily AUC of 400-600 mg·h/L (**Appendix 2**). A loading dose of 25 mg/kg is recommended for all patients with serious infections in the institutional protocol regardless of the initial dosing strategy selected. An AUC of 500 mg·h/L was the

recommended target when designing a regimen, assuming as consensus guidelines recommend, an MIC of 1 mg/L.[23] The decision to order vancomycin levels following the first dose to guide subsequent dosing or to use population estimates to inform an initial maintenance dose is at the discretion of the pharmacist ordering the initial dosing of vancomycin. Two vancomycin concentrations at SS, either peak/trough or two random levels following the SS dose, are included in the dosing protocol to calculate the AUC. SS levels are recommended around the 4th dose of vancomycin, but pharmacists can use their judgement to assess earlier or later based on clinical characteristics or to avoid vancomycin level assessment during sleeping hours. Using these concentrations, we used first-order pharmacokinetic equations as recommended by consensus guidelines to calculate pharmacokinetic parameters and AUC values (**Appendix 2**).[23,97,98]

4.2.3 Statistical Analysis

Patient demographic data are reported as proportions or means/medians, as appropriate per the distribution. AUC target attainment and nephrotoxicity between groups were evaluated using the Chi-Square test. For the analysis of AUC target attainment, logistic regression was used to adjust for any significant differences in relevant baseline characteristics between the two cohorts that may have served as confounders as assessed by study investigators. Continuous data between the first-dose kinetics and empiric dosing group were compared using the independent samples t-test or Wilcoxon rank-sum test depending on the distribution. When comparing CrCl or pharmacokinetic parameters within the same group from baseline to SS, the Wilcoxon signed-rank test was used. Data were analyzed using Stata (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC).

4.3 Results

Of 160 patients admitted to the MICU meeting potential inclusion criteria during the study period, 94 were excluded, with the most common reasons being AKI (n=64) or therapy not continued long enough for SS level evaluation (n=20) (**Figure 4.1**). Sixty-six patients met the full inclusion criteria: 29 patients with first-dose kinetics and 37 patients with empiric vancomycin dosing. All patients received intermittent intravenous infusions of vancomycin.

Baseline characteristics were well-balanced between the two cohorts (**Table 4.1**), with the only significant differences being that patients in the first-dose kinetics group received a slightly higher initial dose of vancomycin compared to the empiric dosing group (2043 ± 449 mg vs. 1568 ± 499 mg; $p<0.001$) and the time from the first dose of vancomycin to the first steady state concentration assessment was slightly longer in the first-dose kinetics group (60 (50-80) hours vs. 47 (37-67) hours; $p=0.018$) compared to the empiric dosing group. Importantly, patients were well-matched on age, baseline renal function (including CrCl), severity of illness, and receipt of concurrent nephrotoxins.

The primary outcome, target AUC target attainment at SS (400-600 mg·h/L), was achieved in 58.6% of first-dose kinetics patients compared to 32.4% with empiric dosing ($p=0.033$). For those not meeting the desired AUC goal, patients in the empiric dosing group were more likely to be subtherapeutic (40.5%) compared to the first-dose kinetics group (3.5%). First-dose kinetics patients, when not achieving AUC target attainment, were more likely to be supratherapeutic compared to the empiric dosing group (37.9% vs. 27.0%). Correspondingly, the median AUC, estimated peak, and trough concentrations were greater in the first-dose kinetics group compared to the empiric dosing cohort. The

minimum and maximum AUC values were numerically more extreme, and the overall variability in AUC at SS was greater (coefficient of variation 40.7% vs. 26.1%), in the empiric dosing group compared to the first-dose kinetics group **(Figure 4.2**). Pharmacokinetic parameters and CrCl at steady state were similar between the two groups (**Table 4.2**). There was no difference between groups in AKI assessed from SS up to 48 hours following collection of vancomycin concentrations at SS.

In simple logistic regression, the use of first-dose kinetics vs. empiric dosing was associated with a 2.95 greater odds of AUC target attainment at SS (OR 2.95 95% CI 1.08-8.10). When adjusted for initial vancomycin dose and time to steady state concentration assessment (neither of which were significantly associated with AUC target attainment in the model), similar results were obtained with a 3.33 greater odds for SS AUC target attainment with first-dose kinetics (OR 3.33 95% CI 1.03-10.72) compared to empiric dosing.

The estimated CrCl increased in both groups from the time of the first dose of vancomycin to SS: from 107 (66-143) to 110 (78-156) mL/min in the first-dose group ($p=0.094$ via pair-wise comparison) and from 109 (73-151) to 141 (98-179) mL/min in the empiric dosing group ($p<0.001$ via pair-wise comparison). In the group of patients with first-dose kinetics, calculated pharmacokinetic parameters were similar between the time of first-dose and SS, with the only exception calculated CL which was greater at the time of first-dose than at SS (**Table 4.3**).

4.4 Discussion

The AUC/MIC ratio is recommended in consensus guidelines as the pharmacokinetic/pharmacodynamic monitoring parameter of choice for vancomycin

when treating MRSA infections.[23] This parameter, related to both efficacy and safety of vancomycin, has particular relevance to critically ill patients who are at high risk of complications from MRSA as well as at high risk of AKI with multiple nephrotoxic risk factors. We showed that patients dosed using a personalized dosing approach with first-dose pharmacokinetics to drive subsequent dosing experienced greater AUC target attainment at SS versus empiric dosing. Although the study was observational in design, the two groups were well-balanced except for two parameters that differed by clinically questionable magnitudes: initial dose of vancomycin differed by approximately 500 mg and time from vancomycin initiation to SS concentration assessment differed by approximately 12 hours. We suspect the longer time to SS concentration evaluation may have been due to pharmacist confidence in the dosing regimen selected given the first-dose pharmacokinetic approach and willingness to wait longer to assess as compared to empiric dosing. Even when adjusted for these differences as potential confounders, the use of first-dose kinetics was consistently associated with a greater likelihood of AUC target attainment at SS. As early and accurate AUC target attainment is increasingly recognized as important in MRSA infections, this approach offers one way to increase the likelihood of AUC target attainment as compared to empiric dosing.

Casapao and colleagues, in a retrospective study of patients with MRSA infective endocarditis, concluded that failure to obtain a day 1 vancomycin AUC/MIC of at least 600 was associated with an increased risk of treatment failure, defined as persistent bacteremia (≥ 7 days) or 30-day attributable mortality.[91] Lodise and colleagues similarly found that day 1 and 2 vancomycin AUC/MIC thresholds (values dependent on MIC methodology) were associated with fewer treatment failures, defined as 30-day mortality,

bacteremia ≥ 7 days, or recurrence.[73] The association of vancomycin AUC with AKI is relevant in the early therapy window as well. In a recent meta-analysis, a vancomycin AUC < 650 mg·h/L on day 1 or 2 was associated with less AKI.[37] Thus, there is a critical need, particularly in an at-risk population such as critically ill patients, for early and accurate attainment of vancomycin AUC to optimize the chance of clinical efficacy and minimize the risk of AKI.

The approach of using patient-specific pharmacokinetic parameters obtained from two serum concentrations following the first dose in designing regimens for vancomycin has produced mixed results.[42,43] In critically ill patients, Truong and colleagues demonstrated that using patient-specific pharmacokinetic parameters derived from two serum concentrations following the first dose of vancomycin resulted in greater goal trough concentrations compared to those patients dosed without first-dose pharmacokinetic monitoring.[43] Conversely, in pediatric patients, first-dose monitoring of vancomycin did not significantly shorten the time to achieve target serum drug concentrations.[42] These prior studies have used trough levels as target attainment, which limits application to some extent in the era of vancomycin AUC-guided dosing. Therefore, we sought to study AUC target attainment at SS in critically ill patients dosed with first-dose kinetics versus empiric dosing.

Similar to Truong et al,[43] we observed greater target attainment in the first-dose group compared to empiric dosing. Neither study demonstrated a reduction in the incidence of AKI with this approach, although both studies were likely underpowered for the outcome of AKI. Our pharmacokinetic parameters calculated and their variability are similar to other published parameters from vancomycin in critically ill adults.[74]

Pharmacokinetic parameters in this patient population were generally similar between the start of vancomycin and SS, further bolstering the validity of using first-dose pharmacokinetic calculations in critically ill patients with relatively stable renal function. This approach was shown to be beneficial for vancomycin, but may have utility with other antibiotics as well such as beta-lactams[99] given the time-critical nature of pharmacokinetic/pharmacodynamic target attainment in critically ill patients. Additionally, this approach may be suitable for high risk patients admitted to non-ICU services. It was recently demonstrated that vancomycin AUC target attainment in patients with MRSA complicated skin and soft tissue infections was associated with timely clinical success and a trend toward a shorter hospital length of stay.[100] Thus, our results could be extrapolated outside of the critically ill patient population to a broader cohort of hospitalized patients with MRSA infection that would benefit from early and precise AUC target attainment.

While this approach demonstrated success in producing goal SS AUC target attainment with a number needed to treat of 4, there are challenges to using this approach that deserve mention. First, if this approach was applied universally, a number of patients would receive therapeutic drug monitoring after the first dose of vancomycin that may go on to receive less than 48 hours of vancomycin therapy. Assuming a patient continues to receive vancomycin until concentrations are assessed at SS, this approach results in 4 vancomycin serum concentrations within a period of days. These costs are combined with the labor costs of pharmacokinetic evaluation, with the realization that overnight evaluation of levels may be required depending on the timing of vancomycin initiation. The pharmacist resources necessary for the potential increase in the need for assessment

of vancomycin concentrations may not exist equally at all hospitals. The use of Bayesian dose optimization tools may help limit the number of required samples if using this approach. The use of first-dose kinetics also requires a presumption of stable renal function at the time of first-dose kinetics and anticipation that renal function will be similar at SS, which may be difficult to predict. Although CrCl increased numerically in both the first-dose kinetics and empiric dosing groups, it was relatively stable from a clinical standpoint from baseline to SS. As such, patients targeted for this approach would need to have presumed stable renal function at the time of vancomycin initiation and anticipated to maintain stable renal function by the time of SS evaluation. Augmented renal clearance has also been noted in sepsis and critically ill patients, which may influence first-dose pharmacokinetic calculations if present and risk over-estimating clearance.[101,102] As noted, a significant number of patients were excluded due to active AKI, which limits the approach of first-dose kinetics. While empiric dosing was more likely to provide subtherapeutic AUC exposure compared to first-dose kinetics, **Figure 4.2** shows a cluster of AUC exposures in the empiric group between 350-400 mg·h/L, which for empiric therapy with no MRSA isolated may be clinically appropriate. However, for severe, confirmed MRSA infection, an AUC of 400-600 mg·h/L would be desired. A high-risk population, either at risk of MRSA isolation or with multiple AKI risk factors, might be identified to benefit most from the patient-specific dosing afforded from obtaining vancomycin serum concentrations following the first dose. This approach is particularly feasible as rapid diagnostics and clinical prediction rules for MRSA continue to be refined. Despite the improved AUC target attainment at SS compared to empiric dosing, the target attainment in the first-dose kinetics group was still limited to

58.6%, which identifies the need for greater precision dosing mechanisms for vancomycin in critically ill patients, potentially including use of continuous infusion.[70] Over one-third of patients in the first-dose kinetics group had AUC values above goal at SS, which may be due to acute changes in pharmacokinetics in critically ill patients. This is another area where application of Bayesian technology may assist with fluctuating renal function that may not meet traditional AKI criteria.

Our study is not without limitations worthy of discussion. First, this study's sample size was known to be small in the design phase due to the finite population of patients with first-dose kinetics and steady state levels, thus the study was underpowered for AKI detection. Clinical efficacy outcomes were not assessed as it was recognized only a fraction of these patients would have true MRSA infection. Second, although the groups were generally similar at baseline, the initial loading dose was slightly higher in the first-dose kinetics group and more time had passed in the first-dose group when SS concentrations were assessed. Prior studies report mixed results on the impact of initial loading dose on target attainment at steady state,[87,103] and the difference between groups was less than 500 mg, which may not be clinically relevant 2-3 days later when SS concentrations are assessed. Additionally, the effect estimate of using the first-dose kinetics strategy was similar when adjusting for initial dose and time to SS concentrations in the logistic regression model. The lower initial dose could indicate non-compliance with institutional dosing protocols in the empiric dosing group. The appropriateness of initial dosing in the empiric group was not assessed in our group, and we acknowledge that clinical judgement may influence a pharmacist's dosing recommendations at the expense of protocol non-compliance.[75] Third, the CrCl increased numerically in both

groups between baseline and SS, but was greater in the empiric dosing group, which may partially explain the greater subtherapeutic AUC values in the empiric dosing group vs. the first-dose kinetics group. There are also are a number of inherent assumptions in using these pharmacokinetic equations, such as the assumption that serum concentrations are obtained at least one half-life apart as well as the fact that two compartment elimination is sometimes possible to observe, particularly if the initial post-dose level is drawn too soon. These assumptions may have contributed to the AUC target attainment in the first-dose kinetics group not being higher. Finally, unmeasured confounders could have biased the results if systemic differences existed between first-dose kinetics and empiric dosing groups aside from pharmacist preference at the time of initial dosing.

4.5 Conclusion

A dosing strategy using two vancomycin serum concentrations following the first dose and calculating personalized pharmacokinetic parameters to guide subsequent dosing is associated with greater AUC target attainment at SS compared to empiric dosing of vancomycin in critically ill adults. Future applications of this strategy to other antibiotics in the ICU, non-ICU patient populations, identification of patients most likely to benefit, and comparison to Bayesian approaches using concentrations after the first dose are future areas for research.

Table 4.1 Patient Demographics

Baseline Characteristics	First Dose Kinetics (n=29)	Empiric Dosing (n=37)	p-value
Age (years)	54.0 ± 17.2	46.6 ± 14.3	0.060
Sex (% male)	15 (51.7%)	20 (54.1%)	0.851
Weight (kg)	84.3 (72.5-106.8)	80.0 (60.4-94.2)	0.165
Initial dose (mg)	2043 ± 449	1568 ± 499	<0.001
Expressed as mg/kg ABW	24 (22-25)	19 (16-23)	<0.001
Serum creatinine at vancomycin initiation (mg/dL)	0.89 ± 0.32	0.91 ± 0.37	0.813
Blood urea nitrogen at vancomycin initiation (mg/dL)	18 (13-30)	19 (13-25)	0.660
Estimated creatinine clearance[a] at vancomycin initiation (mL/min)	107 (66-143)	109 (73-151)	0.841
SOFA score	7.4 ± 3.0	7.3 ± 2.7	0.884
Total daily maintenance dose (mg)	2629 ± 820	2426 ± 1027	0.387
Receipt of concurrent nephrotoxins (%)	23 (79.3%)	24 (64.9%)	0.198
Time from first dose to SS concentration assessment (hours)	59.6 (50.4-79.8)	47.4 (36.5-67.4)	0.018

[a] Calculated using Cockcroft-Gault or Salazar-Corcoran (if weight greater than 125% of ideal body weight). ABW=actual body weight; SOFA=Sequential Organ Failure Assessment; SS=steady state

Table 4.2 Study Outcomes

Outcome	First-Dose Kinetics (n=29)	Empiric Dosing (n=37)	p-value
Achievement of target AUC at steady state (%)	17 (58.6%)	12 (32.4%)	0.033
Below 400 mg·h/L	1 (3.5%)	15 (40.5%)	---
Above 600 mg·h/L	11 (37.9%)	10 (27.0%)	---
AUC at steady state (mg·h/L)	575 (491-722)	438 (379-650)	0.006
Acute kidney injury (%)	4 (13.8%)	4 (10.8%)	0.713
Estimated Trough Concentration (mg/L)	16.4 (12.0-18.7)	11.5 (6.8-17.2)	0.020
Estimated Peak Concentration (mg/L)	36.4 (31.1-41.4)	32.1 (23.6-37.8)	0.049
k_e (hr^{-1})	0.078 (0.047-0.121)	0.070 (0.054-0.126)	0.647
Half-life (hr)	8.9 (5.7-14.7)	9.9 (5.5-12.8)	0.647
Volume of distribution (L)	54.6 (42.2-86.5)	55.6 (39.7-87.8)	0.892
Clearance (L/hr)	4.8 (3.4-5.5)	4.6 (3.1-6.5)	0.811
Creatinine Clearance (mL/min)	110 (78-156)	141 (98-179)	0.072

AUC=area-under-the-curve; k_e=elimination rate constant

Table 4.3 Pharmacokinetic Parameter Comparison Between First-Dose and Steady State in the First-Dose Kinetics Group

Parameter	Time of first dose (n=29)	Steady state (n=29)	p-value
k_e (hr^{-1})	0.084 (0.060-0.115)	0.078 (0.047-0.121)	0.122
Volume of distribution (L)	64.0 (45.0-72.9)	54.6 (42.2-86.5)	0.804
Volume of distribution (L/kg)	0.70 (0.51-0.81)	0.58 (0.45-0.99)	0.689
Clearance (L/hr)	5.0 (4.0-6.5)	4.8 (3.4-5.5)	0.012

k_e=elimination rate constant

Figure 4.1 Flow Diagram for Inclusion and Exclusion

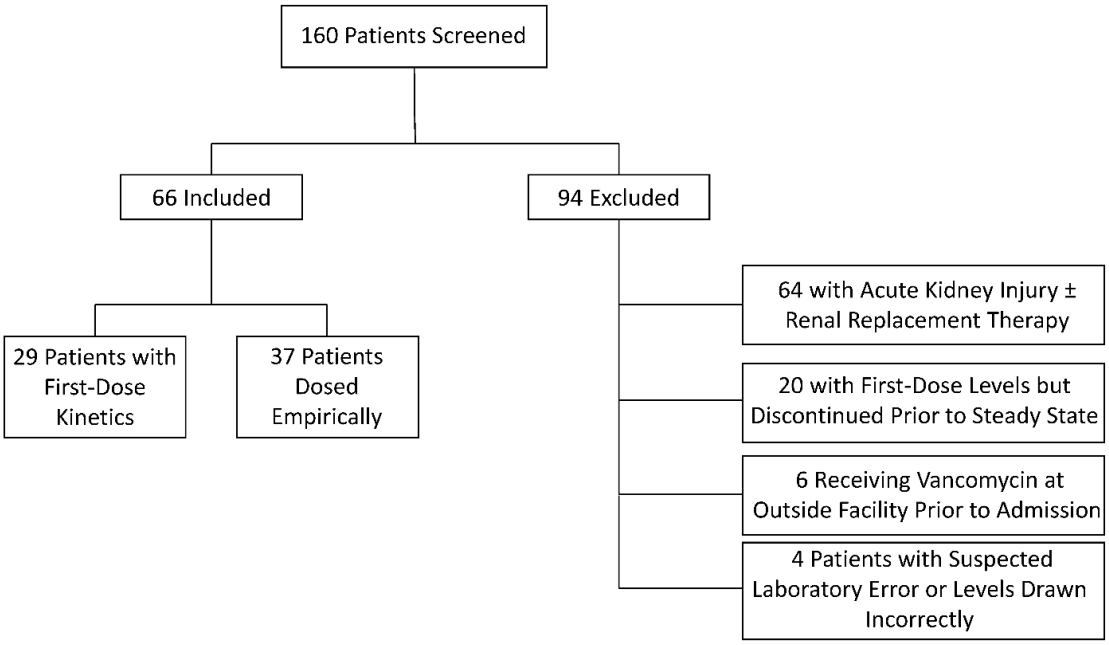
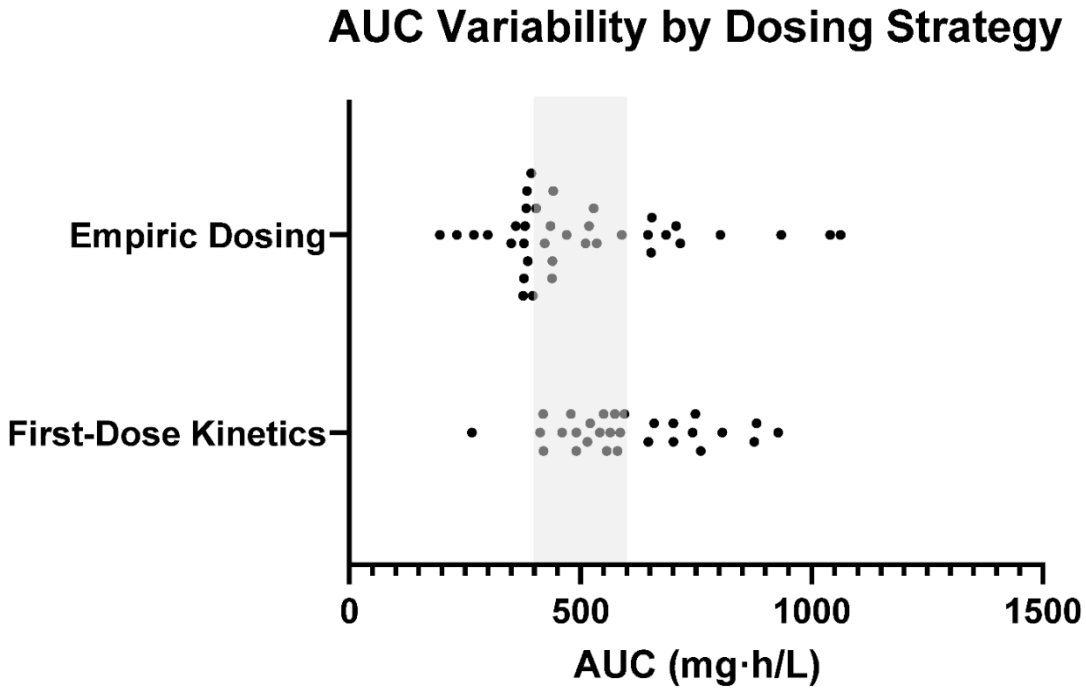


Figure 4.2 AUC Variability and Target Attainment by Dosing Strategy



CHAPTER 5 VANCOMYCIN CONTINUOUS VERSUS INTERMITTENT INFUSION: SYSTEMATIC REVIEW AND META-ANALYSIS

This work has previously been published and permission granted for use in this dissertation by Wolters Kluwer Health, Inc.:

Flannery AH, Bissell BD, Bastin MT, Morris PE, Neyra JA. Continuous Versus Intermittent Infusion of Vancomycin and the Risk of Acute Kidney Injury in Critically Ill Adults: A Systematic Review and Meta-Analysis. *Crit Care Med*. 2020 Jun;48(6):912-918. doi: 10.1097/CCM.0000000000004326.

5.1 Introduction

Vancomycin is one of the most commonly prescribed antibiotics in the inpatient setting, particularly in the intensive care unit (ICU), for empiric coverage of methicillin-resistant *Staphylococcus aureus* (MRSA). Despite extensive clinical experience, a number of questions remain regarding its optimal use, including: pharmacokinetic (PK)/pharmacodynamic (PD) targets translated from experimental models which inform clinicians of optimal drug levels to maximize efficacy of the drug, ideal methods of administration, and techniques to minimize toxicities.[62] The most clinically relevant adverse effect from vancomycin remains acute kidney injury (AKI), and the clinician must balance achieving relevant PK/PD targets with the risk of AKI. Particularly in the vulnerable critically ill patient facing many other kidney insults, the risk of vancomycin-associated AKI may be even higher in this patient population.[104] AKI rates with vancomycin are reportedly as high as 35% when prescribed with other antibiotics, as is commonly done in the ICU.[38] Furthermore, AKI in hospitalized patients is associated with significant increases in mortality, length of stay, and health care costs [105].

Prior work attempting to summarize the effect of continuous versus intermittent vancomycin infusion on AKI in meta-analyses is limited by three main factors: 1.) including a broad mix of patient presentations vastly different from one another (outpatient antimicrobial therapy and ICU patients in the same evaluation) has subsequently lead to conflicting conclusions among meta-analyses, 2.) meta-analytic techniques using raw numbers from observational research rather than odds ratios which more accurately reflect adjustment for confounding factors in the individual studies (if performed), and finally, 3.) prior reports are not inclusive of all available literature given

an increasing trend of publications regarding continuous infusion vancomycin.[56,57,106] We therefore conducted a systematic review and meta-analysis of continuous versus intermittent infusion vancomycin and the associated risk of AKI in critically ill adults.

5.2 Materials and Methods

5.2.1 Search Strategy and Study Selection

With the assistance of an experienced medical librarian, we conducted a systematic search using PubMed/MEDLINE, CINAHL, Web of Science, International Pharmaceutical Abstracts, and Google Scholar from inception to June 2017. References of relevant articles and personal files were also included. A combination of search terms was used, including variants of the following: critical care, intensive care, vancomycin, continuous, and intermittent. We included randomized clinical trials or cohort studies (retrospective or prospective, including quasi-experimental) comparing AKI or nephrotoxicity between continuous and intermittent infusion of vancomycin in adult patients. We only included ICU patients as clearly identified in the study methods. We excluded studies comparing the two regimens in patients on continuous renal replacement therapy given the outcome of interest (AKI) had already occurred. Only peer-reviewed publications were included; conference proceedings were not considered for inclusion. Two authors independently assessed articles for inclusion, with discrepancies resolved via discussion among authors or with the assistance of a third author, if needed. The search was updated in September of 2019. The protocol is registered on PROSPERO 2017:CRD42017053746 and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[107]

5.2.2 Data Extraction, Risk of Bias, and Outcomes

Data elements from included studies were extracted and confirmed by two authors using a standardized table. Variables included: year of study, study design, ICU type, infection type (pathogen and source), definition of AKI/nephrotoxicity, pharmacokinetic goal ranges for both infusion strategies, use of a loading dose, dosing regimen, age, weight, gender, baseline serum creatinine, mean/median daily dose and duration, and frequency of concomitant nephrotoxins.

Risk of bias was assessed with the Cochrane Risk of Bias Assessment Tool for randomized clinical trials and with the Newcastle-Ottawa scale for observational studies.[108,109] Two authors independently assessed risk of bias, with discrepancies resolved via discussion among investigators or with the assistance of a third author, if needed.

The primary outcome was AKI/nephrotoxicity, as defined according to each study's definitions. Mortality was assessed as a secondary outcome, as was % target attainment for the pharmacokinetic goal (typically a trough level for intermittent infusion and plateau level for continuous infusion) set by the dosing protocol in the study. Data were extracted for these binary outcomes as both counts as well as odds ratio (OR) with 95% confidence intervals (CI). If an adjusted analysis was performed, the OR and 95% CI were extracted from the adjusted analysis reported for a study. If the data were presented as counts, the OR and 95% CI was manually calculated.

5.2.3 Data Synthesis and Analysis

Meta-analyses were performed using RevMan v5.3 (The Cochrane Collaboration, Oxford, UK) and R (R Foundation for Statistical Computing, Vienna, Austria) using the

meta package.[110] The risk of publication bias was assessed with the use of a funnel plot and Harbord test.[111] The generic inverse variance method was used to pool ORs from each included study for AKI and mortality. The Mantel-Haenszel method was used for proportions with count data for percentage target attainment for the pharmacokinetic secondary outcome. Heterogeneity was assessed with the I^2 statistic. Given the anticipated heterogeneity in study designs and definitions, a random effects model was selected as the most conservative approach.

5.3 Results

5.3.1 Search Results and Study Characteristics

Following removal of duplicates from the search strategy, 311 unique citations were screened for inclusion. A large portion of these (n=121) were excluded for only evaluating one method of infusion strategy. Of the 29 studies remaining following application of the exclusion criteria, 6 studies did not meet criteria to be classified as studying critically ill patients. Of the 23 studies remaining, 11 met criteria for inclusion in the analysis of the primary outcome. Complete search results and identification of included studies are shown in **Figure 5.1**.

We identified 11 total studies published over a 23 year period, which evaluated 2,123 patients for the primary outcome of AKI.[54,55,71,112-119] Study characteristics, demographics, and definitions are provided in **Table 5.1**. Two studies were randomized trials, 3 were prospective observational, and 6 were retrospective cohort studies. Collectively, the studies investigated a wide range of ICU populations including medical, surgical, trauma, neurologic, cardiac, and burns. While some studies focused on a particular type of infection, the majority of studies evaluated a range of common

infections in the ICU setting. While the definitions of nephrotoxicity differed across study groups, all but 3 studies included an increase of serum creatinine by 50% from baseline as at least part of the definition.[54,55,71,112-119] Dosing targets for single concentrations (continuous group) and troughs (intermittent) varied, but the most common recurring targets were 20-25 mg/L for continuous infusion and a trough of 15-20 mg/L for intermittent dosing. Loading doses were more commonly noted in the continuous infusion group. Initial dosing regimens varied across studies as well, with 15 mg/kg q8-12h being the most common in the intermittent group and 30 mg/kg/day the most common in the continuous group. Duration of treatment ranged from approximately 1-2 weeks in many of the studies. Patients were predominately male and, when reported, were commonly exposed to different nephrotoxic medications.

5.3.2 Risk of Bias

A complete table with the risk of bias assessments is included in **Table 5.2**. The randomized clinical trials both had at least two areas at high risk of bias,[54,55] notably with regard to blinding of participants/personnel and incomplete outcome data. Six of the observational studies were classified as low risk of bias (scored of 7-9), 3 studies as high risk of bias (score of 4-6), and none as very high risk of bias (score of 0-3).[71,112-120] A funnel plot (**Figure 5.2**) suggests minimal publication bias. This was confirmed with the Harbord test (p=0.66).[111]

5.3.3 Acute Kidney Injury

The incidence and OR for study outcomes are displayed in **Table 5.3**. The pooled OR suggests an association between continuous infusion of vancomycin and a reduction in AKI when compared to intermittent infusion of vancomycin (OR 0.47; 95% CI 0.34-

0.65) and is shown in **Figure 5.3**. Heterogeneity was fairly low with I^2 of 15%. In sensitivity analysis, the observational studies (n=9) contribute heavily to the overall findings (OR 0.44; 95% CI 0.31-0.63) compared to the randomized controlled trials (n=2) (OR 0.72; 95% CI 0.30-1.73) (**Figure 5.4**). A sensitivity analysis was also performed to assess the risk of bias in contributing to the findings. For those studies deemed to be low risk of bias (randomized trials and those observational studies with a Newcastle-Ottawa score ≥ 7) (n=8), the OR for AKI with continuous infusion was less pronounced (OR 0.52; 95% CI 0.33-0.82) in comparison to those studies deemed high risk of bias (n=3) (OR 0.37; 95% CI 0.22-0.61), but both analyses were statistically significant favoring continuous infusion to attenuate the risk of AKI (**Figure 5.5**). Additional sensitivity analysis assessing the impact of AKI/nephrotoxicity criteria comparing more sensitive definitions such as 50% increase in serum creatinine from baseline with more severe definitions such as need for renal replacement therapy yielded similar point estimates (**Figure 5.6**). In order to assess the impact of target trough concentrations in the intermittent arm and evaluate if higher troughs were possibly contributing to elevated area-under-the-curve (AUC) drug exposure, a sensitivity analysis was performed based on the target trough concentration: higher (15-20 mg/L) or lower (5-15 mg/L) (**Figure 5.7**). Point estimates were again similar and statistically significant in both groups. Finally, in order to assess the impact of time and practice changes in regard to vancomycin dosing targets, a cumulative meta-analysis was conducted (**Figure 5.8**). As the pooled estimate was updated with each additional study, particularly during the time period 2001-2013, the beneficial effects of continuous infusion evolved and stabilized at the current point estimate.

5.3.4 Mortality

Eight of the 11 included studies evaluated mortality, either as ICU or overall hospital mortality. There was no association between the infusion strategy of vancomycin and mortality in critically ill patients (OR 1.04; 95% CI 0.80-1.35) (**Figure 5.9**). Low heterogeneity was present (I^2 0%).

5.3.5 Pharmacokinetic Target Attainment

Five of the included studies assessed in a dichotomous fashion the frequency with which the infusion strategy resulted in the goal pharmacokinetic target attainment for the protocol. These targets were a given concentration range for troughs for intermittent infusion and a single level range for continuous infusions. As compared to intermittent infusion, continuous infusion was associated with a 2.63 greater odds of pharmacokinetic target attainment (OR 2.63; 95% CI 1.52-4.57) (**Figure 5.10**). Moderate heterogeneity was present (I^2 45%).

5.4 Discussion

This study represents the most focused systematic review and meta-analysis investigating the risk of AKI when comparing continuous with intermittent infusion of vancomycin in critically ill adults. The pooled estimates indicate the use of continuous infusion as compared to intermittent infusion of vancomycin is associated with an approximate 50% reduction in the odds of AKI. Given the ubiquity of vancomycin use in critically ill patients and the substantial morbidity and costs associated with AKI, the method of administration may have important effects on the drug safety profile without altering efficacy. Indeed, we found no difference in our secondary outcome of mortality between the two infusion strategies.

Our study has many strengths, including the robust search strategy and focused patient selection that allowed us to examine the effects of infusion strategy in critically ill adults. Additionally, our meta-analytic techniques allowed us to pool adjusted Ors rather than raw, unadjusted numbers from prior reports. This is the most likely explanation why our study suggested a beneficial effect of continuous infusion vancomycin while a prior meta-analysis did not, as this method of data extraction and analysis is particularly important for a large cohort study under consideration that reported different effects on AKI in unadjusted and adjusted analysis.[57,71]

As recently demonstrated in an animal model, the AUC and maximum concentration (C_{max}) of vancomycin during the dosing interval are most associated with injury biomarkers of AKI, specifically kidney injury molecule-1 (KIM-1).[121] These data offer a potential mechanism to suggest a scientific rationale for the findings of our meta-analysis: by avoiding high peak concentrations of vancomycin through delivery via a continuous infusion rather than intermittent dosing, the risk of vancomycin-associated AKI may be minimized. These markers of kidney injury were found in animals despite only 24 hours of exposure to vancomycin, thus the potential benefits of continuous infusion may be relevant to not only definitive MRSA therapy, but empiric therapy as well. In addition to the potential safety benefit, continuous infusion of vancomycin may be advantageous compared to intermittent infusion for other reasons. We found continuous infusion was associated with much greater pharmacokinetic target attainment (as dictated by the study's dosing protocol) when compared to intermittent infusion. Given the anticipated guideline change to recommend AUC (as opposed to trough) monitoring for vancomycin,[23] continuous infusion has many advantages. Vancomycin

monitoring costs may be minimized with continuous infusion (1 level required for evaluation) compared to intermittent infusion (2 levels required for evaluation). Additionally, dosing adjustments require far fewer assumptions and calculations and are vastly simplified with the continuous infusion approach. Continuous infusion may offer superior AUC/MIC target attainment over the dosing interval with less variability and thus optimize the delivery of vancomycin.[122] Practically, a loading dose of 15-25 mg/kg is often recommended, followed by the maintenance dose infused over 24 hours. Following infusion of the drug for 24-48 hours and assuming relatively stable renal function, a level can be drawn and multiplied by 24 to obtain the AUC exposure.

Despite these possible advantages, certain barriers may limit the adoption of continuous infusion of vancomycin in all critical care settings. In an experiment involving human umbilical vein endothelial cells, vancomycin given continuously was noted to cause more endothelial cell toxicity compared to intermittent infusion.[123] The Infusion Nurses Society identifies vancomycin as an intermediate-risk vesicant based on conflicting data.[124] Given this, some institutions will choose to limit continuous infusion to central line administration only while others have successfully reported peripheral administration at concentrations of 6 mg/mL or less.[113] Drug compatibility issues may also arise depending on availability of intravenous access when continuously infusing vancomycin.

This systematic review and meta-analysis is not without limitations. First, the majority of studies included in this systematic review and meta-analysis are observational, which limits their validity in comparison to prospective randomized trials. The two randomized trials we did include have possible biases as well as limited sample

size (n=174 combined). However, the sensitivity analysis including only low risk of bias studies revealed a similar point estimate to the primary analysis, suggesting that while the data may be observational in nature, high risk of bias observational studies are not driving the primary findings. Similarly, many important infectious diseases clinical issues in critical care related to Staphylococcal infections have limited, or no, randomized controlled trial data to guide clinician decision making, including: AUC versus trough based dosing for vancomycin,[23] nephrotoxicity risk of combination vancomycin and piperacillin-tazobactam,[125] cefazolin versus nafcillin for methicillin-susceptible *Staphylococcus aureus* infections,[126] and combination therapy for MRSA bacteremia.[127] Second, one emerging observation is AUC-based dosing of vancomycin is associated with reduced AKI compared to trough-based dosing, particularly given growing evidence that trough values correlate poorly with AUC and troughs of 15-20 mcg/mL may provide supratherapeutic exposure when assessed by the AUC.[36,128] The possibility cannot be ruled out that continuous infusion is associated with less AKI in our analysis because continuous infusion regimens in these studies perhaps better controlled AUC within a therapeutic range without predisposing to elevations in AUC (despite trough concentrations at goal). However, the sensitivity analysis in the cohort targeting lower trough concentrations in the intermittent groups still found a statistically significant difference favoring a continuous infusion. Third, the AKI definition was not universal among all included studies and most were based on serum creatinine as the primary classification. However, the sensitivity analysis including studies with a definition of 50% serum creatinine increase from baseline or 0.3-0.5 mg/dL increase from baseline (including 9 of the 11 studies) essentially mirrors the Kidney Disease Improving Global

Outcomes (KDIGO) stage 1 serum creatinine criteria for AKI,[79] and the point estimate in **Figure 5.6** mirrors that of the primary analysis. Finally, variations in the empiric dosing protocol and adjustment strategies introduce additional heterogeneity among studies. For example, more frequent loading doses in the continuous infusion group may have contributed to the association with greater percentage of pharmacokinetic target attainment (as defined by the dosing protocol used) with the continuous infusion strategy.[129] It is also important to note that pharmacokinetic attainment was not the primary outcome of our systematic review and meta-analysis, thus other studies may exist that studied pharmacokinetic target attainment in critically ill patients, but did not include the primary outcome of AKI, that were excluded from our analysis.

Future studies should consider urinary biomarkers of tubular damage, such as KIM-1, as a mechanistic outcome comparing the two dosing strategies. Given that critically ill patients face many other potential insults to the kidney, controlling for severity of illness, use of vasopressors, concurrent nephrotoxins, relevant past medical history, and other factors should be carefully considered. AUC monitoring should be used as the dosing target as opposed to a single level or trough evaluation, with a goal of 400-600 mg*hr/L.[23] A standardized definition and grading of AKI as proposed by KDIGO should be employed,[79] potentially with additional risk stratification as assessed by urinary biomarkers of tubular injury and dysfunction.[130]

5.5 Conclusions

In a meta-analysis of critically ill adults receiving vancomycin, continuous infusion was associated with a 53% reduction in the odds of AKI compared to intermittent infusion. Given the growing recognition that peak levels, when administered via intermittent

infusion, may be contributing to sub-clinical and clinical AKI, additional prospective trials of continuous vs. intermittent infusion of vancomycin with AUC-targeted dosing are warranted to optimize the safety of vancomycin for critically ill patients.

Table 5.1 Study Demographics

Reference	Study Design	ICU Type	Infection	Definition of Acute Kidney Injury/Nephrotoxicity	Target (mg/L)		Loading Dose		Dosing Regimen	
					CI	II	CI	II	CI	II
Akers 2012	Cohort (retrospective)	Burn	Pathogen: 33.3% Gram-positive Source: Multiple	≥0.5 mg/dL or ≥50% increase in SCr	20-25	Ctr=15-20	None	None	3,000 mg/day	1,000 mg q8h
Bissell 2018	Cohort (retrospective)	Trauma	Pathogen: 21% MRSA Source: Multiple	SCr increase 1.5 times baseline or absolute increase in SCr ≥ 0.3 mg/dL	15-25	Ctr=15-20	20 mg/kg	NR	30 mg/kg/day	NR
Duszynska 2016	Cohort (prospective)	Unspecified	Pathogen: Non-MRSA gram positive Source: Multiple	SCr increase of ≥ 0.3 mg/dL or 1.5 to 2 times increase from baseline on at least 2 consecutive days and/or urine output < 0.5 mL/kg/hr for >6 hours	15-20	Ctr=15-20	500 mg	25 mg/kg	30mg/kg/day	Nomogram based on weight and CrCl
Hanrahan 2014	Cohort (retrospective)	All	Pathogen: 11% MRSA Source: Unspecified	SCr increase ≥ 50%; eGFR decrease ≥ 25%; SCr ≥ 3.95 mg/dL	NR	NR	NR	NR	NR	NR
Hong 2015	Cohort (retrospective)	Neurosurgical	Pathogen: 16% *S. aureus* Source: Multiple	≥ 50% increase in SCr; SCr > 0.5 mg/dL from baseline; ≥50% decrease in CrCl on at least 2 consecutive days	20-30	Ctr =15-20	20 mg/kg	None	15-40 mg/kg/day depending on CrCl	15 mg/kg q8-24h depending on CrCl
Hutschala 2009	Cohort (retrospective)	Cardiac surgery ICU	Pathogen: Staphylococcus species Source: Multiple	≥50% increase in SCr in 48 hours; ≥0.3 mg/dL rise in SCr in 48 hours; <0.5 mL/kg/hr urine output > 6 hours	20-25	Ctr=15	20 mg/kg	20mg/kg	36 mg/kg/day	NR
Saugel 2013	Cohort (retrospective)	Medical ICU	Unspecified	Need for renal replacement therapy	15-25	Ctr: 5-10	1000-1250mg	None	60 mg/hr (1440 mg/day) Impaired renal function: 40 mg/hr (960 mg/day)	1000-2000 mg daily
Schmelzer 2013	Randomized Clinical Trial	Trauma	Pathogen: NR Source: Pneumonia	SCr increase ≥ 50% from baseline	15-25	Ctr: 15-20	20 mg/kg	None	21.6-57.6 mg/kg/day per nomogram	15 mg/kg q12h
Tafelski 2015	Cohort (prospective)	Surgical ICU	Pathogen: Not reported Source: Multiple	RIFLE criteria for injury, failure, or loss	15-20	Ctr: 10-20	1000mg	Recommended (details NR)	500mg-2000 mg/day depending on CrCl	500 mg q6h or 1000 mg q12h
Wysocki 1995	Cohort (prospective)	Unspecified	Pathogen: MRSA Source: pneumonia, bacteremia	Rise in SCr of 0.5 mg/dL or more if initial level <3 mg/dL Rise of 1 mg/dL or more if initial level ≥ 3 mg/dL	20-30	Cpk=20-40 Ctr=5-10	15 mg/kg	None	30 mg/kg/day	15 mg/kg q12h
Wysocki 2001	Randomized Clinical Trial	Medical-Surgical	Pathogen: Methicillin-resistant Staphylococci Source: Multiple	50% increase in SCr from day treatment was started to end of treatment	20-25	Ctr=10-15	15mg/kg	None	30 mg/kg/day	15 mg/kg q12h

Table 5.1 (continued)

Reference	Regimen (%)		Age (years)		Weight (kg)		Males (%)		Baseline Serum Creatinine (mg/dL)		Mean/Median Daily Dose[a]		Mean/Median Duration (days)[a]		Concomitant Nephrotoxins (%)	
	CI	II	CI	II	CI	II	CI	II	CI	II	CI	II	CI	II	CI	II
Akers 2012	49	51	40.8 ± 19.8	35.6 ± 17.2	89.4 ± 20.8	91.3 ± 21.5	91	90	0.99 ± 0.39	0.97 ± 0.40	2,500 mg ± 720 mg	2,290 mg ± 630mg	12.4 ± 11.8[b]	13.3 ± 12.4[b]	NR	NR
Bissell 2018	50	50	43 ± 16	52 ± 18	87 ± 26	87 ± 20	87	73	0.7 (0.54-0.88)	0.81 (0.68-1.1)	2500 (1991-3000)	2000 (2000-2698)	3.8 (2.7-6.8)	6.8 (3.5-9.2)	98.7	97.3
Duszynska 2016	50	50	62 ± 14	54 ± 15	77 ± 11	84 ± 10	81	86	1.0 ± 0.6	1.1 ± 0.7	2219 ± 476	2466 ± 930	7 (7-8)	7 (7-10)	86	100
Hanrahan 2014	46	28[c]	59 (44-69)	61 (48-71)	75 (66-85)	75 (68-88)	64	67	NR	NR	1700 mg (1200-2100 mg)	1500 mg (900-2200 mg)	5.3 (3.4-10.3)	4.4 (2.5-7.3)	72[d]	45[d]
Hong 2015	50	50	56 ± 15.5	56.3 ± 14.8	79.8 ± 18.3	82.3 ± 25.5	54	55	0.92 ± 0.31	0.98 ± 0.49	2572 ± 784	2779 ± 1205	10.4 ± 7.8	14.1 ± 8.8	NR[e]	NR[e]
Hutschala 2009	80	20	59 ± 14	59 ± 14	75 ± 16	75 ± 16	61	70	0.9 ± 0.5	0.9 ± 0.7	1935 mg ± 688 mg	1325 mg ± 603 mg	9 ± 6	8.5 ± 7	71.4[d]	73.3[d]
Saugel 2013	69	31	65 ± 13	61 ± 15	75 (50-130)	70 (46-100)	61	67	NR	NR	960 mg (526-1723 mg)	500 mg (180-1000mg]	6 (2-21)	7 (1-24)	59[d]	57[d]
Schmelzer 2013	51	49	40.3 ± 16.4	41.3 ± 17.9	82.8 ± 21.2	87.2 ± 19.6	89	89	0.72 ±0.20	0.79 ± 0.21	NR	NR	NR	NR	NR[e]	NR[e]
Tafelski 2015	61	39	60 (50-70)	67 (48-75)	70 (60-90)	80 (70-90)	59	69	NR	NR	NR	NR	7 (4-11)	5 (3-8)	NR	NR
Wysocki 1995	50	50	61 ± 17	67 ± 13	68 ± 10	70 ± 7	77	77	1.28 ± 0.93	1.62 ± 0.63	24 ± 14mg/kg	12 ± 5mg/kg	16 ± 10	16 ± 13	NR	NR
Wysocki 2001	51	49	64 ± 13	62 ± 16	73 ± 15	69 ± 17	69	60	1.1 ± 0.5	1.0 ± 0.4	Values NR but similar between groups	Values NR but similar between groups	13 ± 5	14 ± 6	59	74

ICU = intensive care unit; CI = continuous infusion; II= intermittent infusion; MRSA = Methicillin-resistant *Staphylococcus aureus*; SCr = serum creatinine; Cpk = peak concentration; Ctr = trough concentration; NR = not reported

[a]Means reported as means ± standard deviation and medians as median (interquartile range)
[b]Reported only for GPC bacteremia cohort
[c]Not add up to 100 due to classification of a mixed category as well
[d]Included vasopressors
[e]Not reported but all patients with nephrotoxicity were receiving concomitant nephrotoxins

Table 5.2 Risk of Bias Assessment

Study									
			Randomized Clinical Trials Cochrane Risk of Bias Assessment						
	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias		
Schmelzer 2013	Low	Unclear	High	Low	High	High	High		
Wysocki 2001	Low	Low	High	Low	High	Unclear	Low		
			Observational Studies Newcastle-Ottawa Scale						
	Representativeness Of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not presented at start of study	Comparability of cohorts on the basis of design or analysis	Assessment of Outcomes	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	Total
Akers 2012	*	*	*	0	0	*	*	*	6
Bissell 2018	*	*	*	0	0	*	*	*	6
Duszynska 2016	*	*	*	0	**	*	*	*	8
Hanrahan 2014	*	*	*	0	**	*	*	0	7
Hong 2015	*	*	*	0	**	*	*	*	8
Hutschala 2009	*	*	*	*	**	*	*	*	9
Saugel 2013	*	*	*	0	0	*	*	0	5
Tafelski 2015	*	*	*	0	*	*	*	*	7
Wysocki 1995	*	*	*	0	*	*	*	*	7

Table 5.3 Study Outcomes

Reference	Acute Kidney Injury/ Nephrotoxicity			Mortality			Pharmacokinetic Target Attainment %	
	CI	II	OR[a]	CI	II	OR[a]	CI	II
Akers 2012	7/68 (10.3%)	13/70 (18.6%)	0.50 (0.19-1.35)	13/68 (19.1%)	14/70 (20%)	0.95 (0.41-2.19)	21/68 (30.9%)	16/70 (22.9%)
Bissell 2018	16/75 (21.3%)	32/75 (42.7%)	0.36 (0.18-0.75)	7/75 (9.3%)	13/75 (17.3%)	0.49 (0.18-1.31)	45/75 (60%)	30/75 (40%)
Duszynska 2016	5/21 (23.8%)	8/21 (38.1%)	0.51 (0.13-1.93)	NR	NR	NR	15/21 (71.4%)	9/21 (42.9%)
Hanrahan 2014	161/653 (24.7%)	77/390 (19.7%)	0.12 (0.04-0.35)	172/653 (26.3%)	49/390 (12.6%)	1.36 (0.90-2.05)	NR	NR
Hong 2015	10/65 (15.4%)	14/65 (21.5%)	0.66 (0.27-1.62)	10/65 (15.4%)	13/65 (20.0%)	0.72 (0.29-1.80)	26/65 (40%)	14/65 (21.5%)
Hutschala 2009	33/119 (27.7%)	11/30 (36.7%)	0.66 (0.28-1.54)	25/119 (21%)	6/30 (20%)	1.06 (0.39-2.89)	NR	NR
Saugel 2013	7/94 (7.4%)	12/52 (23.1%)	0.27 (0.10-0.73)	NR	NR	NR	NR	NR
Schmelzer 2013	1/28 (3.6%)	3/27 (11.1%)	0.30 (0.03-3.04)	NR	NR	NR	16/28 (57.1%)	2/27 (7.4%)
Tafelski 2015	20/76 (26.3%)	17/49 (34.7%)	0.67 (0.31-1.47)	15/76 (19.7%)	11/49 (22.4%)	0.85 (0.35-2.04)	NR	NR
Wysocki 1995	2/13 (15.4%)	3/13 (23.1%)	0.61 (0.08-4.41)	5/13 (38.5%)	6/13 (46.2%)	0.73 (0.15-3.47)	NR	NR
Wysocki 2001	10/61 (16.4%)	11/58 (19.0%)	0.84 (0.33-2.15)	21/61 (34.4%)	19/58 (32.8%)	1.08 (0.50-2.31)	NR	NR

[a]Adjusted OR reported with 95% confidence intervals if available from study; otherwise manually calculated from raw data

Figure 5.1 Study Inclusion and Exclusion

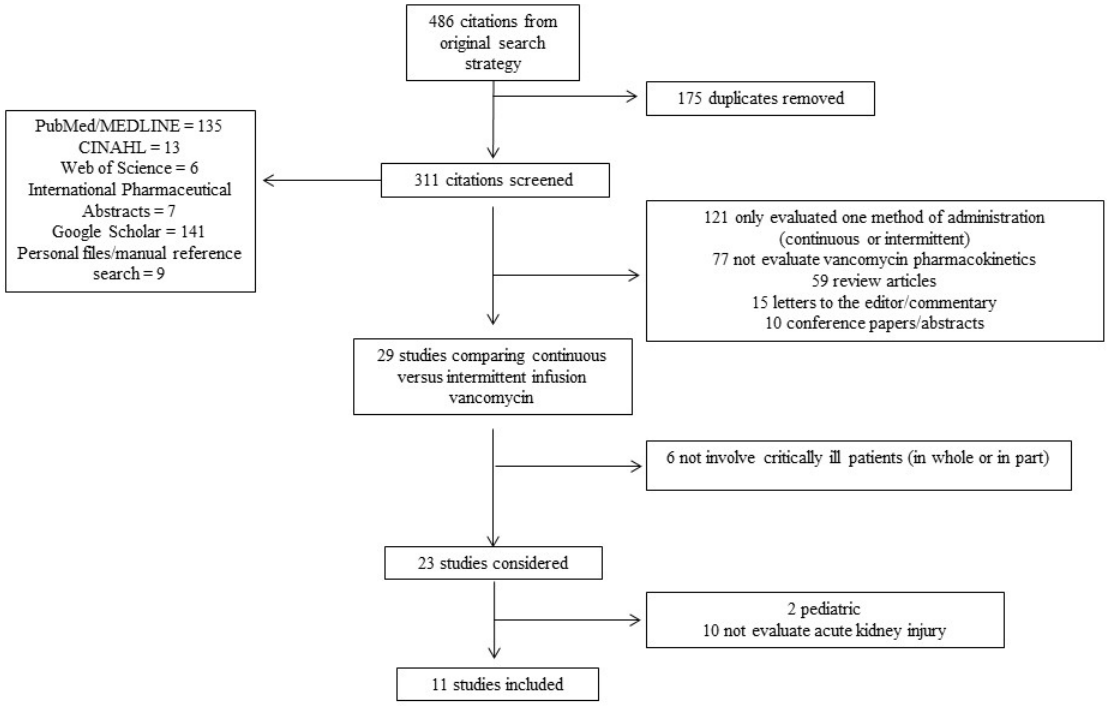


Figure 5.2 Funnel Plot to Assess Publication Bias

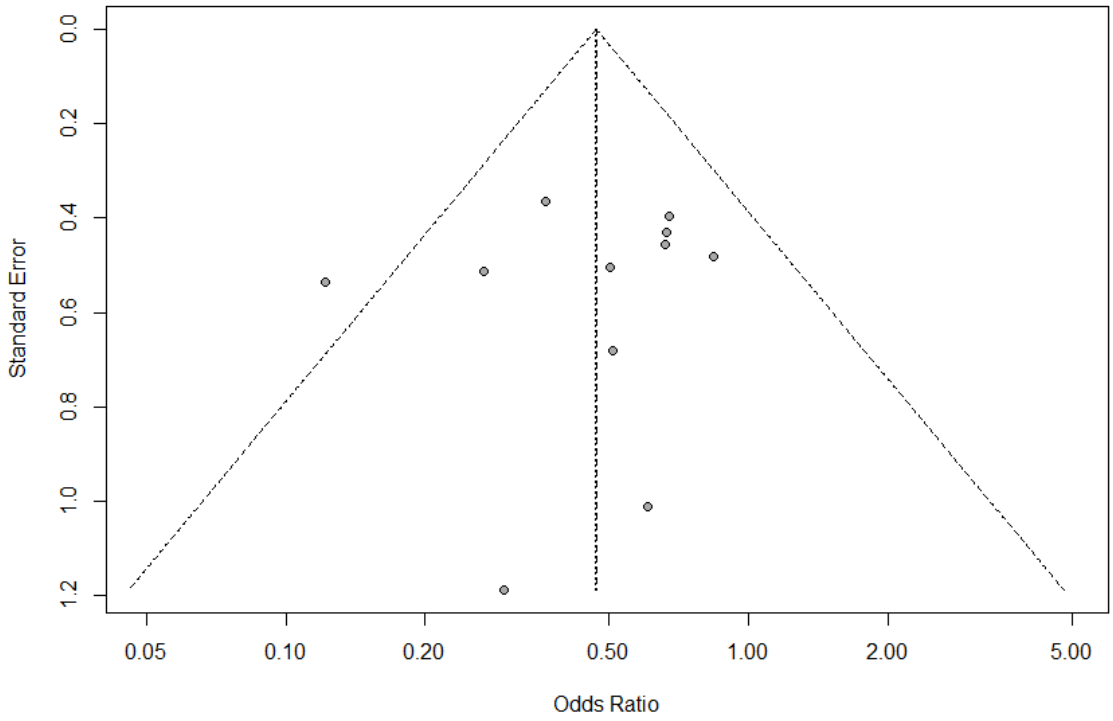


Figure 5.3 Forest Plot for Primary Outcome of Acute Kidney Injury/Nephrotoxicity

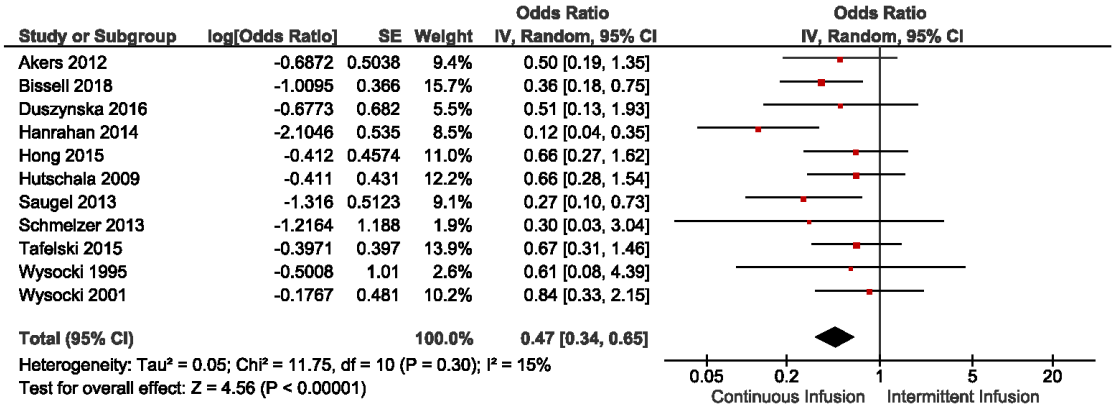
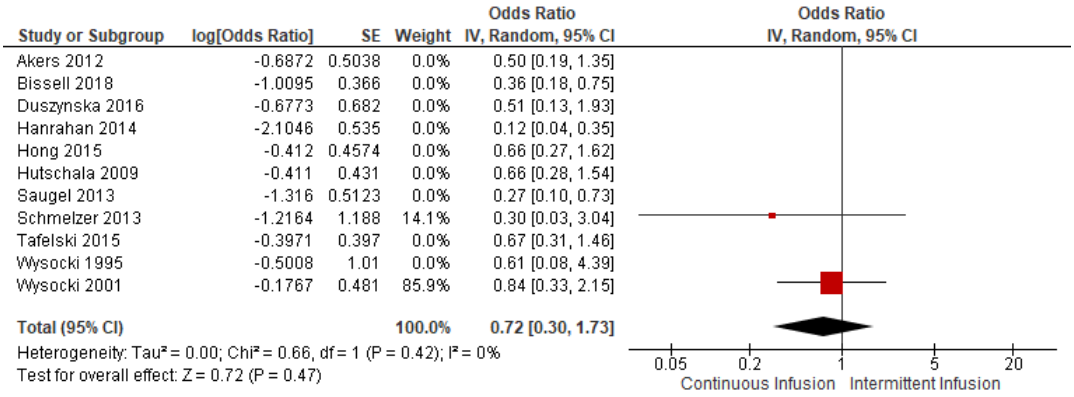


Figure 5.4 Sensitivity Analysis: Impact of Study Design on Outcome of AKI

Randomized Controlled Trials (n=2)



Observational Studies (n=9)

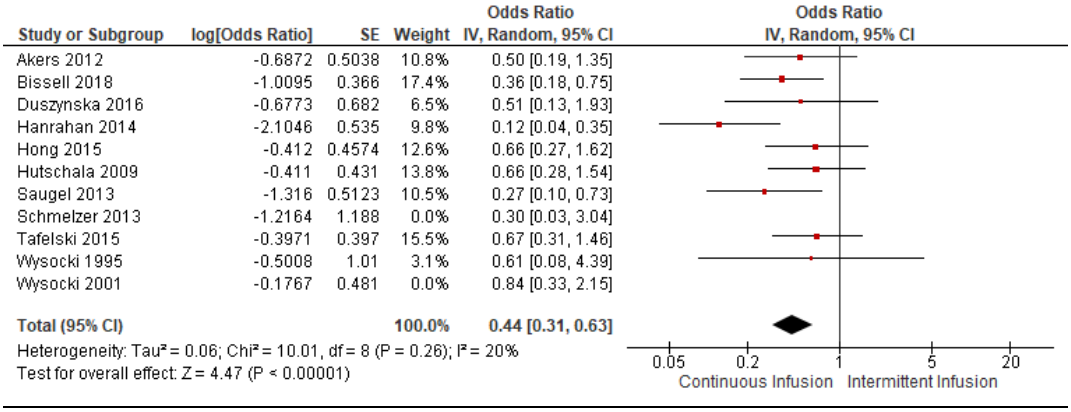
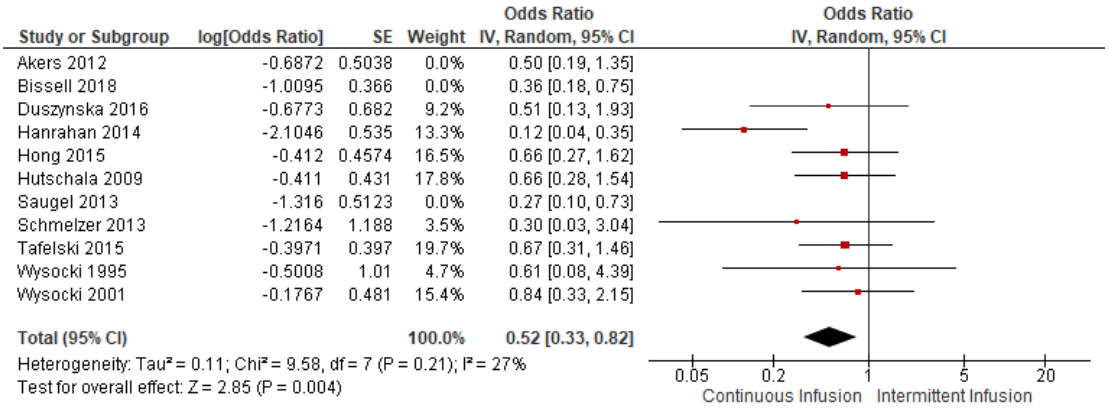


Figure 5.5 Sensitivity Analysis: Impact of Risk of Bias on Outcome of AKI

Low Risk of Bias (n=8)



High Risk of Bias (n=3)

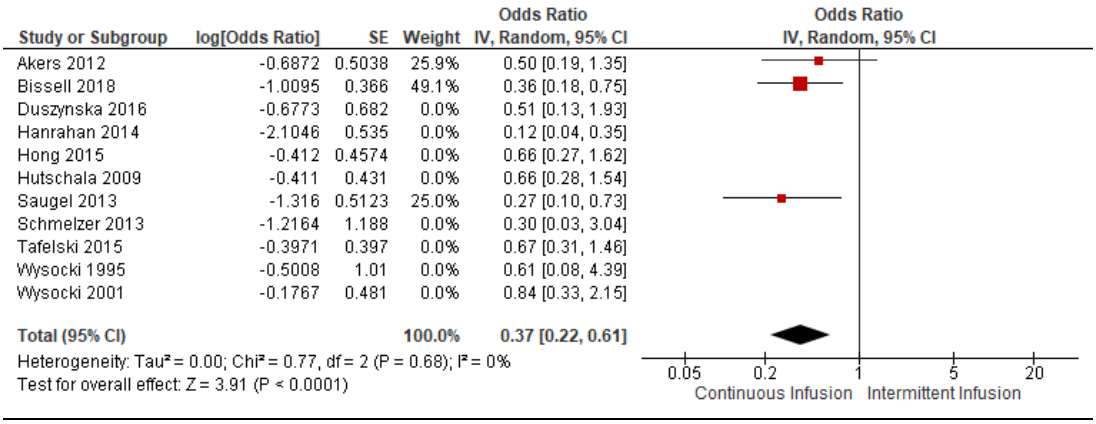
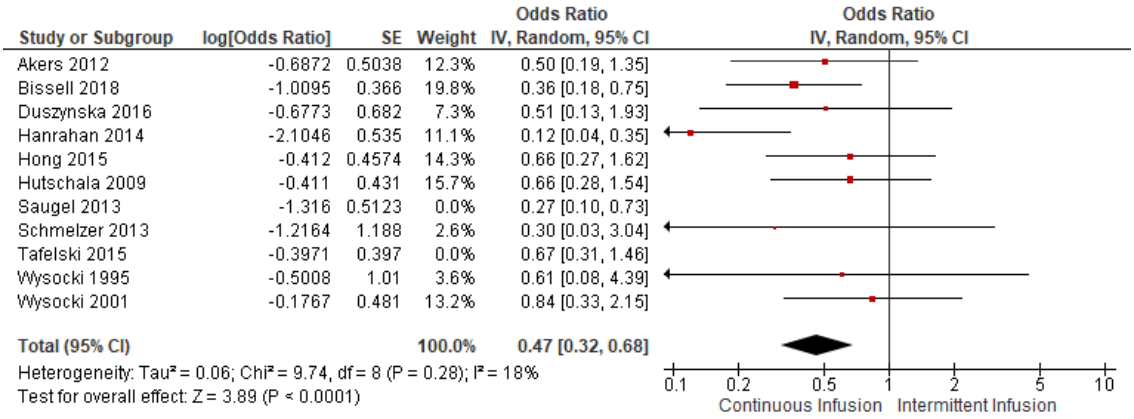


Figure 5.6 Sensitivity Analysis: Impact of AKI/Nephrotoxicity Criteria on Outcome of AKI

Less Severe Definition: 50% Serum Creatinine Increase From Baseline or 0.3-0.5 mg/dL Increase From Baseline (n=9)



More Severe Definition: Injury, Failure, or Loss Criteria or Need for Renal Replacement Therapy (n=2)

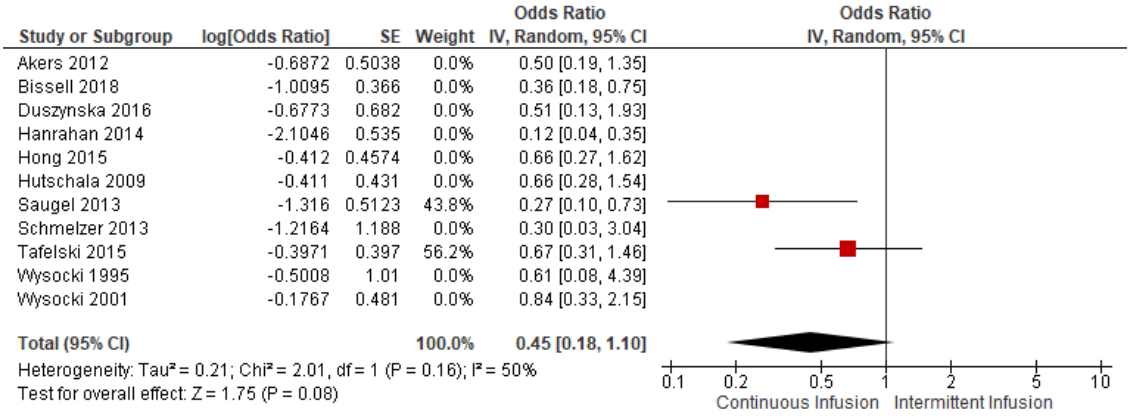
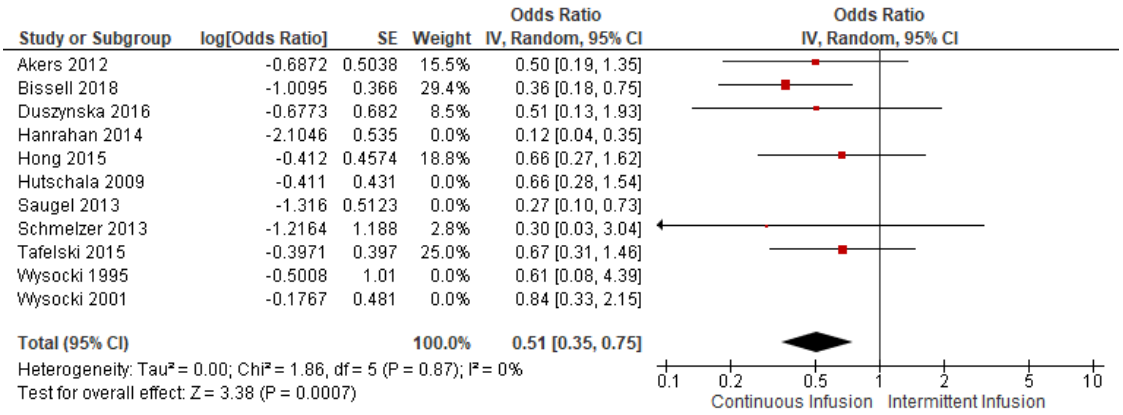


Figure 5.7 Sensitivity Analysis: Assessment of Vancomycin Trough Target on Outcome of AKI

Intermittent Trough Target: 15-20 mg/L (n=6)



Intermittent Trough Target: 5-15 mg/L (n=4)

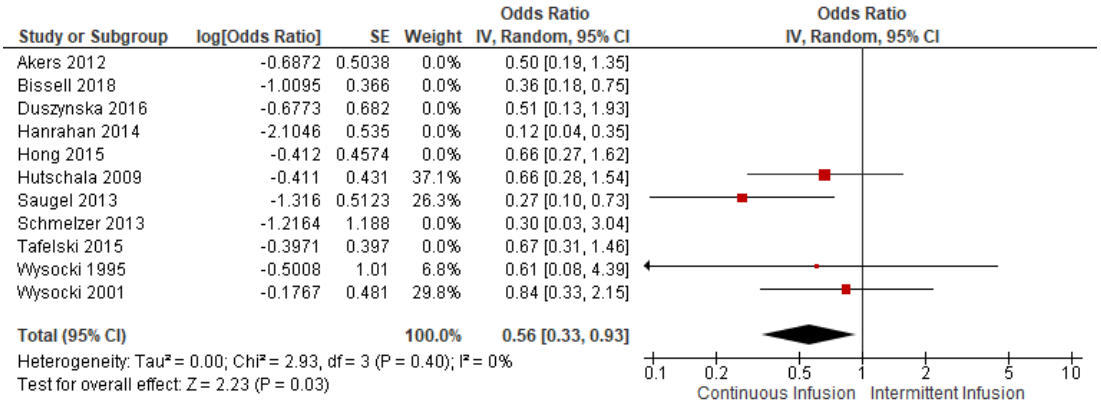


Figure 5.8 Cumulative Meta-Analysis by Year

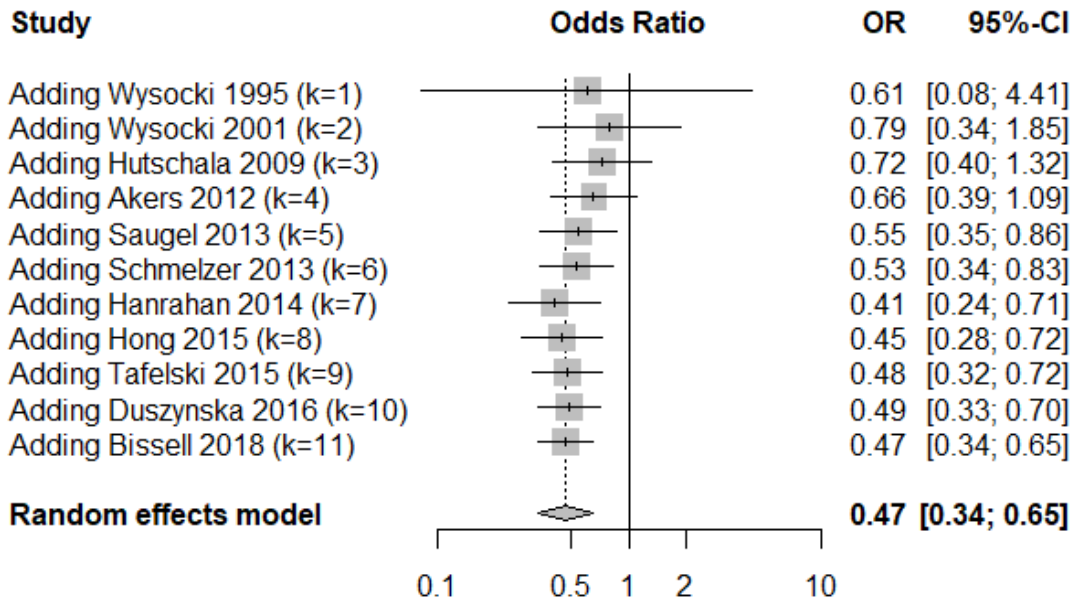


Figure 5.9 Assessment of Vancomycin Infusion Strategy on Mortality

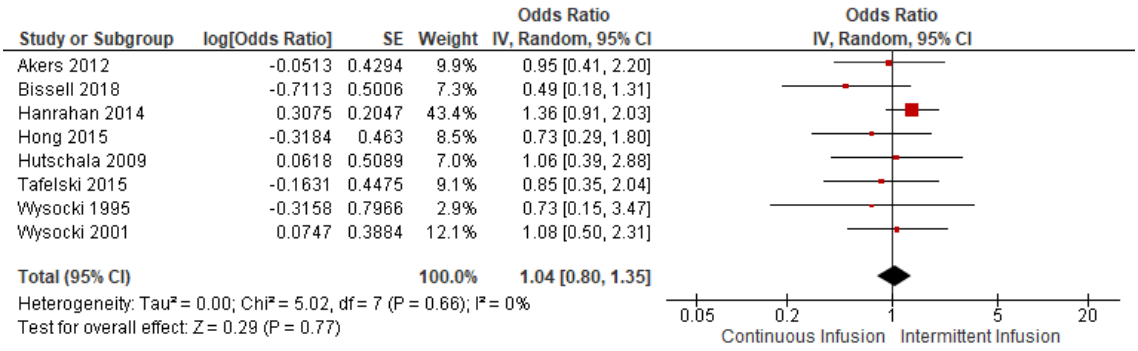
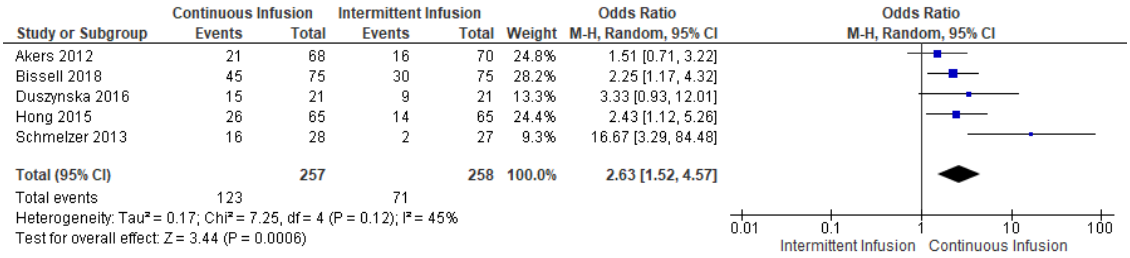


Figure 5.10 Assessment of Vancomycin Infusion Strategy on Pharmacokinetic Target Attainment



CHAPTER 6 POPULATION PHARMACOKINETIC MODEL OF CONTINUOUS INFUSION VANCOMYCIN

6.1 Introduction

In a recent survey of critical care practitioners, continuous infusion vancomycin was identified as rarely used by 94.2% of respondents.[75] Continuous infusion vancomycin offers many advantages to intermittent infusion, including fewer concentration assessments and less complex mathematical calculations for AUC monitoring,[131] greater consistency in steady state concentrations,[132] and importantly, potentially less acute kidney injury.[70] A number of population pharmacokinetic models have been developed for vancomycin administered via intermittent infusion in critically ill patients.[133] However, likely given the low reported frequency of use, less pharmacokinetic modeling has been performed on continuous infusions of vancomycin in this patient population.[134] In our recent meta-analysis of continuous versus intermittent infusion of vancomycin in critically ill adults,[70] we noticed that while intermittent infusions of vancomycin are typically dosed via nomogram, it was less common to personalize dosing for continuous infusion and a dose of 30 mg/kg/day was most commonly used. When comparing these two infusion strategies head-to-head, it seems necessary that we would compare precise dosing of intermittent infusion with precision dosing of continuous infusions. Accordingly, we sought to develop a population pharmacokinetic model of continuous infusion vancomycin in critically ill adults.

6.2 Methods

6.2.1 Study Design

This was a prospective, observational study of continuous infusion vancomycin in a medical intensive care unit (ICU) of a tertiary care, academic referral center from June 2019 to February of 2020. Vancomycin dosing and monitoring at the University of

Kentucky is established by a Pharmacy and Therapeutics committee approved protocol that authorizes pharmacists to adjust doses and order vancomycin concentrations. As part of our institutional shift from trough to AUC-based monitoring,[94] continuous infusion vancomycin was instituted in the protocol for consideration in critically ill patients, patients requiring >4,000 mg vancomycin per day, or those unable to obtain therapeutic AUC on intermittent infusions. The decision to use continuous or intermittent infusion at this time was based on the discretion of the pharmacist dosing and monitoring vancomycin. Continuous infusion was only advised for use with patients deemed to have stable renal function, and a loading dose of vancomycin 25 mg/kg was recommended if employing a continuous infusion. Administration via a central line was recommended if available, but based on other data using < 6 mg/ml concentrations, peripheral administration was allowed.[113] Adult patients were prospectively identified during this time period, and included if they received a continuous infusion of vancomycin and had serum vancomycin concentrations drawn during routine clinical care. Patients requiring continuous renal replacement therapy were excluded. The study was approved by the Institutional Review Board at the University of Kentucky with a waiver of informed consent (#56908).

6.2.2 Data Collection

Data were collected as documented in the electronic medical record. All doses, time stamps, and vancomycin serum concentrations were extracted to build the model data file. Covariates collected for evaluation in the pharmacokinetic model included: age, race, sex, height, weight, Sequential Organ Failure Assessment score, serum creatinine, creatinine clearance (Cockcroft-Gault[95] unless >125% ideal body weight then Salazar-

Corcoran[96]), serum blood urea nitrogen (BUN), serum sodium, serum chloride, serum phosphorous, serum albumin, presence of cirrhosis, norepinephrine equivalents, and cumulative fluid balance in hospital stay.

6.2.3 Laboratory Analysis

Serum vancomycin samples were analyzed in the hospital's clinical laboratory using a Roche Cobas kinetic interaction of microparticles in a solution (KIMS)-based immunoassay (Roche Diagnostics Corporation, Indianapolis, IN). All other laboratory parameters were obtained from documentation during routine clinical care.

6.2.4 Pharmacokinetic Modeling

Pharmacokinetic modeling was performed in Monolix using non-linear mixed effects modeling with the Stochastic Approximation Expectation-Maximization (SAEM) algorithim.[135,136] Complete data were present for all doses and concentrations assessed. Covariate values present at the time of initial vancomycin dose were used for covariate modeling in Monolix.

6.2.5 Structural Model

The structural model for the data was determined by testing one- and two-compartment models, with elimination rate constant or clearance models, and with linear or Michaelis-Menten elimination assuming lognormal distributions of parameters with random effects. Parameter estimation is based on minimizing the objective function value (OFV) using maximum likelihood estimation.[60,137] Because more complex models with additional parameters offer more degrees of freedom for the model to take different shapes and therefore better able to describe the data, it is necessary to account for the additional parameters when comparing structural models using the Akaike information criterion and

Bayesian information criterion (BIC) with the following where OBJ is the minimum OFV, η_p is the number of parameters in the model, and N is the number of data observations.[60]

$$AIC = OBJ + 2 \cdot \eta_p$$

$$BIC = OBJ + \eta_p \cdot Ln(N)$$

Since BIC penalizes for greater model complexity, and therefore may be preferable when data are limited, we primarily used BIC for comparing structural models in addition to visual review of observed vs. predicted plots, scatter plot of residuals, and individual subject model fits.[60] We used the classification of Kass and Raftery to assess model differences in BIC, with differences of >10 deemed "very strong" evidence in factor of the model with the lower BIC.[60,138]

6.2.6 Covariate Selection

The relationship between covariates and the parameter estimates was assessed with Pearson's correlation tests or analysis of variance (ANOVA) for continuous and categorical variables, respectively. Using power law relationships, continuous covariates were log-transformed using the following formula: log (covariate divided by the weighted mean of the dataset). Clearance and volume were allometrically scaled for weight using fixed coefficients of 0.75 and 1, respectively.[139,140] Covariate selection was further informed by the COnditional Sampling use for Stepwise Approach based on Correlation tests (COSSAC) algorithm in Monolix.[135]

6.2.7 Error Model

Once the covariates for inclusion were identified, the residual error model was developed using the Stochastic Approximation for Model Building Algorithm in Monolix testing a

constant, proportional, or combined error model.[135,141] Reiterations of the model were performed until the optimized model was found as assessed using BIC_c.

6.2.8 Final Model

The final model was selected based on the change in OBJ, with a reduction of 3.84 considered statistically significant ($p<0.05$, chi squared distribution, degree of freedom =1), lowest AIC and BIC scores, goodness-of-fit checks including individual patient review of observed vs. predicted, between subject variability associated with population estimates, and the rule of parsimony.

6.2.9 Simulations

Using population estimates from the final population pharmacokinetic model, Monte-Carlo simulations were performed in Simulx[142] assessing AUC target attainment of 400-600 mg·hr/L for three discrete time intervals: AUC_{0-24}, AUC_{24-48}, and AUC_{48-72}. These time intervals were selected given the importance of early AUC target attainment within initial days of therapy, but also since empiric therapy in the ICU setting is often 48-72 hours in duration. Given vancomycin is typically dosed on a mg/kg basis clinically, and extremes of weight may lead to issues of dose capping, we simulated individuals of more typical weights of 70-100 kg. Drawing from a similar distribution of age (mean 55 ± 16) and BUN (23.1 ± 16.6 mg/dl) as our population, we first simulated 1000 patients with the typical recommendation of a 25 mg/kg loading dose and 30 mg/kg/day maintenance dose to begin immediately following the completion of the loading dose. The initiation timing of the maintenance dose in relation to the loading dose was examined to determine the impact of delaying the start of the maintenance dose on AUC target attainment. Using identified covariates from the population pharmacokinetic model, we attempted to

develop a simplified dosing nomogram for continuous infusion vancomycin considering these covariates. This process was iteratively repeated in 5 mg/kg/day intervals for the loading and maintenance doses, seeking the combination that maximized AUC target attainment within 72 hours while attempting to limit the frequency of supratherapeutic AUCs at any given time point to <25% if possible.

6.3 Results

As noted in the inclusion criteria, all patients were critically ill and admitted to the medical ICU. Patient demographics are shown in **Table 6.1**. The data consist of 239 dosing events and 124 vancomycin concentrations from 50 critically ill patients. Nine patients had two serum concentrations assessed following the loading dose, while an additional eight patients had a single serum concentration assessed following the loading dose, prior to any subsequent dosing.

6.3.1 Structural Model

All structural models assessed are shown in **Table 6.2**. The structural model selected was a one (1) compartment model using the parameters volume (V) and clearance (CL). As seen in **Table 6.2**, we considered the difference in BIC of >10 between this and the next closet model very strong evidence in favor of this model as described in our methods.[60,138] Visual inspection revealed acceptable observed vs. predicted concentrations, individual fits of the model to concentrations from each subject, appropriate distribution of the residuals, and acceptable relative standard errors (RSEs) of the parameter estimates.

6.3.2 Covariate Selection

Figure 6.1 shows correlations between covariates and the parameter estimates for V and CL. Statistical comparisons are shown in **Table 6.3.** In addition to allometrically scaled weight using fixed values of 0.75 and 1 for clearance and volume, respectively, covariates retained in the final model included serum BUN and age with significant effects on clearance.

6.3.3 Error Model

The best residual error model identified was the proportional error model shown below, where Cc is the predicted concentration, b represents the error model parameter, and e is a standard normal random variable that generates the residual error.[141]

Observation = Cc + b*Cc * e

6.3.4 Final Model

Given significant between subject variability for volume when modeled as a random effect, volume was modeled as a fixed effect in the final model using the allometrically scaled weight. The final model is shown below, where η_{Cl} is the random effect of clearance.

$\log(V) = \log(V_{pop}) + \beta_{V\_logWT} * logWT$

$\log(CL) = \log(CL_{pop}) + \beta_{Cl\_logAGE} * logAGE + \beta_{Cl\_logBUN} * logBUN + \beta_{Cl\_logWT} * logWT + \eta_{CL}$

The final population parameter estimates for the model are shown in **Table 6.4**. The observed vs. predicted concentrations are shown in **Figure 6.2** for the population predictions (R^2=0.26) and individual predictions (empirical Bayes estimates) (R^2= 0.60;

outlier proportion=5.65%). The residuals are appropriately distributed as shown in **Figures 6.3 and 6.4**. The distribution of CL is shown in **Figure 6.5** (shrinkage -7.63%). Distribution of the CL standardized random effect is shown in **Figure 6.6** and is appropriately centered around zero. Assessment of model convergence was appropriate (**Figure 6.7**).

6.3.5 Simulations

Using population parameters and the final population pharmacokinetic model and simulating 1000 patients weighing between 70-100 kg with the traditional recommendation of a 25 mg/kg loading dose followed by 30 mg/kg/day continuous infusion, we observed a high frequency of supratherapeutic AUC_{0-24}, AUC_{24-48}, and AUC_{48-72} values (**Table 6.5**). This is shown graphically in **Figure 6.8**, where the median concentration of the continuous infusion is just under 30 mg/L, while a continuous infusion steady state concentration of 17-25 mg/L (multiplied by 24) corresponds to AUC values within 400-600 mg·hr/L. We observed that extending the time from the start of the loading dose to initiation of the continuous infusion maintenance dose allowed for optimization of AUC across the time periods evaluated, particularly avoiding supratherapeutic AUC_{0-24} (**Table 6.5).** Using the iterative process described to maximize AUC target attainment while attempting to keep the frequency of supratherapeutic AUC exposure to <25% at each time period, if possible, we determined that the optimal regimen of vancomycin continuous infusion for a typical individual weighing 70-100kg was a 20 mg/kg loading dose (dosed on actual body weight) followed by a continuous infusion of 20 mg/kg/day to begin 12 hours following the initiation of the loading dose. In a simulated population with a similar distribution of age and serum BUN as our

population used for model development, this regimen achieved AUC target attainment at 24, 48, and 72 hours 58.4%, 40.7%, and 37.9% of the time, respectively, while minimizing the frequency of supratherapeutic AUC exposure to under 25%. The simulated concentration versus time profile and AUC_{0-24}, AUC_{24-48}, and AUC_{48-72} for this regimen are shown in **Figures 6.9** and **6.10**, respectively.

Given that serum BUN, age, and weight were identified as significant covariates, we attempted to develop a simplified dosing nomogram using these covariates. Based on our simulations, we designed the maintenance dose of continuous infusion to begin 12 hours following the start of the loading dose. Age and BUN were categorized as above or below their mean values from the covariate distribution and simulated in the following categories: age (18-55), age (56-80), BUN (≤ 23 mg/dl) and BUN (24-75 mg/dl). The two-by-two nomogram created that maximized AUC target attainment and attempted to limit supratherapeutic AUC frequency to <25% is shown in **Table 6.6**. Given that we modeled volume as a fixed rather than random effect, we kept the 20 mg/kg loading dose constant in the proposed nomogram. This simplified nomogram demonstrates improved simulated AUC_{0-24}, AUC_{24-48}, and AUC_{48-72} target attainment compared to the universal 20mg/kg loading, 20 mg/kg/day maintenance regimen derived in **Table 6.5**.

6.4 Discussion

Using data from 50 patients in a medical ICU receiving continuous infusion vancomycin, we were able to fit a population model to the data that reasonably explained the vancomycin concentrations observed. A one-compartment model with clearance and volume was the best fit, with covariate adjustments for serum BUN, age, and weight.

In 2011, Roberts and colleagues published a population pharmacokinetic model of continuous infusion vancomycin.[143] Similar to our model, the final model was a one-compartment model with clearance and volume. Total body weight was a significant parameter in describing volume of distribution and urinary creatinine clearance best described vancomycin clearance. Compared to our model, their estimate of population clearance was slightly higher (mean 4.58 L/hr). While the R^2 of our observed vs. individual predicted concentrations was similar at 0.60 in each study, our observed population vs. predicted concentrations was improved (R^2=0.26 vs. 0.07), suggesting our model may perform superior for empiric dosing of vancomycin in this population.[143] The exact type of ICU patient in the model (surgical vs. medical) developed by Roberts et al[143] is unclear, but may explain their higher clearance. For example, trauma and neurocritically ill patients may be at a higher likelihood of augmented renal clearance and have additional comorbidities impacting vancomycin clearance compared to a medically critically ill patient population such as ours. A similar one-compartment model was developed in 2017 parameterized by clearance and volume.[144] Creatinine clearance was included as a covariate influencing vancomycin clearance and total body weight as a covariate impacting volume. Additionally, mechanical ventilation, tested for its potential biologic rationale of lowering cardiac output and renal blood flow, was included with a significant covariate effect on vancomycin clearance.[144]

Several other comparisons between these prior models and our model deserve discussion. First, although components of typical creatinine clearance equations including age and weight were included in our model, creatinine clearance was not a significant covariate of vancomycin clearance as it was compared to the prior two models

discussed.[143,144] Models can only describe the data they are developed from, and patients in our cohort likely represent a population deemed to have relatively stable renal function for the pharmacist dosing to use continuous rather than intermittent infusions, which is supported by the baseline serum creatinine and BUN from **Table 6.1**. From this cohort however, we did observe BUN as the strongest covariate effect on vancomycin clearance. BUN was not evaluated in the prior models developed.[143,144] BUN is often concomitantly measured with serum creatinine as a measure of renal function; approximately 85% of the body's urea is eliminated by the kidney.[145] Just as serum creatinine is identified as a relatively insensitive marker to loss of renal function, several factors in critical care can influence BUN including protein intake and liver disease to name a few.[145] Even though BUN is a recognized poor marker of GFR, its elevation is associated with mortality in several disease states and may reflect on tubular function of the kidneys to some extent as well, which is also known to influence vancomycin secretion.[146,147] Second, unlike other models that modeled volume as a random effect, the between subject variability in volume led us to model volume as a fixed effect. Despite our efforts to capture potential measurable covariate influencers of this parameter, including cumulative fluid balance, we were unable to account for the variability of this parameter, which is known to exhibit significant variability in critically ill patients, with both inter-and intra-patient variability depending on clinical status.[148]

Our simulations performed using this model provide additional insights into optimal continuous infusion vancomycin dosing. Although it is recognized that a loading dose of vancomycin is advisable when using continuous infusions due to the potential delay in reaching appropriate concentrations with a continuous infusion, the optimal

combination and relative timing of loading and maintenance initiation are not abundantly clear based on published literature. Updated vancomycin consensus guidelines recommend a loading dose of 20-35 mg/kg vancomycin (up to 3,000mg) if considering intermittent dosing, although at the time of vancomycin initiation it may be unclear whether intermittent or continuous infusion regimen will be pursued, particularly if started in the emergency department for example where the patient is originally assessed.[23] If using continuous infusion vancomycin, consensus recommendations suggest consideration of a loading dose of 15-20 mg/kg and a maintenance dose of 30-40 mg/kg/day.[23] Our findings agree with a component of this recommendation, in that we found greater AUC target attainment over 72 hours, with reduced frequency of supratherapeutic AUC with a lower loading dose of 20 mg/kg. Additionally, our simulations suggested that delaying the initiation of the maintenance dose to 12 hours following the start of the loading dose also maximized AUC target attainment while minimizing supratherapeutic $AUC_{0\text{-}24}$ that may have been due to administration of the maintenance dose beginning immediately following the loading dose. This is highly clinically relevant and suggests that the decision to initiate maintenance dosing for continuous infusion can be delayed for 12 hours while other important elements occur, including any transitions of care and further evaluation of intravenous access, which may be a critical consideration to use continuous vancomycin or not. Contrary to the model by Roberts[143] and consensus guideline recommendations,[23] our simulations suggest significantly lower maintenance doses of vancomycin in medically critically ill individuals. While we determined a maintenance dose of 20 mg/kg/day optimized the probability of AUC target attainment while minimizing supratherapeutic exposure on

average, we saw much greater success with the simplified nomogram we developed using weight-based dosing with the covariates of serum BUN and age that we derived from our model. In a previous study involving a similar medically critically ill population, we found AUC target attainment to only be 32.4% with empiric intermittent infusion dosing, which was increased to 58.6% with the use of first-dose pharmacokinetics.[149] Our proposed nomogram, if validated, would provide potentially even greater precision and accuracy, with far fewer labor and laboratory costs, to optimize AUC target attainment over the initial days of therapy.

Our study has several strengths, including the vancomycin concentration-to-patient ratio of almost 3:1 and large number of biologically relevant covariates investigated for a drug known to exhibit substantial inter-patient variability. Our final population pharmacokinetic model was able to well-describe the observed versus individual predicted serum vancomycin concentrations. We simulated clinically relevant scenarios to help inform optimal dosing of continuous infusions and were able to derive a simplified nomogram that could assist with empiric vancomycin dosing when given via continuous infusions. Several limitations deserve mention as well. First, these are data from a single ICU at a single center and a relatively small number of patients. Second, this model, including our proposed nomogram, has not been externally validated. While the model and covariates deserve additional study for validation, the covariates in our model are static on the day of vancomycin initiation and changes during critical illness may influence the impact of these covariates have on the final model. More sophisticated approaches with covariate modeling may allow us to increase the precision of the model.

6.5 Conclusion

We developed a population pharmacokinetic model of continuous infusion vancomycin in critically ill adults which adequately described the data using a one-compartment model with volume and clearance, and covariates of serum BUN, age, and weight. A simplified dosing nomogram optimized AUC target attainment over the initial 72 hours of therapy using these covariates. Future research to validate this model can help to inform precision dosing of continuous infusions of vancomycin in critically ill patients.

Table 6.1 Patient Demographics at Time of First Vancomycin Dose

Patient Characteristic (n=50)	**Descriptive Statistics[a]**
Age (years)	59 (46.5-68)
Race (% white)	46 (92%)
Sex (% male)	27 (54%)
Height (cm)	167.6 (162.9-177.8)
Weight (kg)	90.7 (64.2-109.1)
Sequential Organ Failure Assessment score	6 (5-9)
Serum creatinine (mg/dl)	0.8 (0.6-1.0)
Serum blood urea nitrogen (mg/dl)	20 (13-27)
Serum sodium (mmol/l)	140 (137-142)
Serum chloride (mmol/l)	104 (100-107)
Serum albumin (g/dl)	2.5 (2.0-2.9)
Serum phosphorus (mg/dl)	2.7 (2.2-3.4)
Cirrhosis (%)	8 (16%)
Norepinephrine equivalents (mcg/kg/min)	0 (0-0.03)
Net fluid balance (ml)	-102 (-906 to 798)
Initial vancomycin dose (mg)	2000 (1500-2500)
Initial vancomycin dose (mg/kg actual body weight)	22 (17-24)

[a]Reported as medians (interquartile range) or percentages

Table 6.2 Evaluation of Structural Model

Run	Compartment	Elimination	Parameters	OFV	AIC	BIC	BIC_c
01	1	Linear	V, k	829.8	841.8	853.3	856.9
02	1	Linear	V, Cl	815.6	827.6	839.1	842.7
03	1	MM	V, K_m, V_m	826.7	842.7	858.0	862.6
04	2	Linear	V_1, Q, V_2, Cl	813.5	833.5	852.6	858.1
05	2	Linear	V, $k_{1,2}$, $k_{2,1}$, k	814.0	834.0	853.1	858.6
06	2	MM	V_1, Q, V_2, K_m, V_m	812.7	836.7	859.6	866.0
07	2	MM	V, $k_{1,2}$, $k_{2,1}$, Km, Vm	822.1	846.1	869.0	875.4

OFV= -2 x log-likelihood; AIC= Akaike Information Criteria; BIC= Bayesian Information Criteria; BIC_c= Corrected Bayesian Information Criteria; k=elimination rate constant; V= volume of distribution; Cl= Clearance; MM=Michaelis-Menten; K_m= Michaelis constant; V_m=maximum rate; V_1= central compartment; V_2=peripheral compartment; Q=intercompartmental clearance; $k_{1,2}$=rate of transfer from central to peripheral compartment; $k_{2,1}$=rate of transfer from peripheral to central compartment

Table 6.3 Statistical Evaluation of Covariates with Random Effects

V

	COEFF	**STATISTICS**	**P-VALUE**
LIVER		0.058	8.1e-1
RACE		0.76	4.73e-1
SEX		0.92	3.42e-1
AGE	0.023	0.16	8.75e-1
ALBUMIN	-0.0025	-0.018	9.86e-1
BUN	-0.2	-1.43	1.59e-1
CHLORIDE	-0.04	-0.28	7.82e-1
CRCL	0.16	1.13	2.66e-1
FLUID BALANCE	0.0064	0.044	9.65e-1
HT	0.052	0.36	7.21e-1
SODIUM	-0.2	-1.43	1.6e-1
PHOS	-0.2	-1.4	1.68e-1
SCR	-0.15	-1.02	3.15e-1
SOFA	-0.16	-1.09	2.79e-1
VASOPRESSORS	0.022	0.15	8.8e-1
WT	0.32	2.35	**2.28e-2**

Table 6.3 (con)

CL

	COEFF	STATISTICS	P-VALUE
LIVER		0.15	7.03e-1
RACE		0.046	9.55e-1
SEX		2.29	1.36e-1
AGE	-0.26	-1.89	**6.43e-2**
ALBUMIN	-0.015	-0.1	9.2e-1
BUN	-0.45	-3.48	**1.08e-3**
CHLORIDE	-0.12	-0.83	4.12e-1
CRCL	0.35	2.61	**1.21e-2**
FLUID BALANCE	0.17	1.2	2.35e-1
HT	0.24	1.75	**8.71e-2**
SODIUM	-0.18	-1.25	2.16e-1
PHOS	-0.28	-1.99	**5.22e-2**
SCR	-0.15	-1.05	2.99e-1
SOFA	-0.085	-0.59	5.55e-1
VASOPRESSORS	-0.14	-0.95	3.45e-1
WT	0.37	2.76	**8.08e-3**

Table 6.4 Population Pharmacokinetic Parameter Estimates

	Value	Standard error	Relative standard error (%)
Fixed Effects			
V_{pop}	44.37	3.46	7.81
β_{V_logWT}	1		
Cl_{pop}	4.18	0.2	4.74
β_{Cl_logAGE}	-0.35	0.13	38.3
β_{Cl_logBUN}	-0.3	0.074	25.2
β_{Cl_logWT}	0.75		
Standard Deviation of the Random Effects			
ω_{Cl}	0.28	0.037	13.5
Error Model Parameters			
b	0.26	0.022	8.26

Table 6.5 Area-Under-the-Curve Target Attainment for Tested Loading and Maintenance Dose Combinations Using Monte-Carlo Simulations

Loading Dose	Maintenance Dose	AUC_{0-24}	AUC_{24-48}	AUC_{48-72}
Loading Dose Over 2.5 Hours Immediately Followed by Initiation of Continuous Infusion				
25 mg/kg	30 mg/kg/day	Goal: 8.2% Sub: 10.5% Supra: 81.3%	Goal: 27% Sub: 8.2% Supra: 62.0%	Goal: 21.5% Sub: 10.4% Supra: 65.9%
25 mg/kg	25 mg/kg/day	Goal: 11.3% Sub: 10.9% Supra: 77.8%	Goal: 30.5% Sub: 15.6% Supra: 50.7%	Goal: 35.3% Sub: 16.8% Supra: 44.2%
20 mg/kg	25 mg/kg/day	Goal: 20% Sub: 13.2% Supra: 66.8%	Goal: 34.2% Sub: 16.4% Supra: 45.9%	Goal: 38% Sub: 16.4% Supra: 41.7%
25 mg/kg	20 mg/kg/day	Goal: 16.4% Sub: 12.2% Supra: 71.4%	Goal: 32.8% Sub: 33.3% Supra: 30.5%	Goal: 37% Sub: 36.2% Supra: 22.9%
20 mg/kg	20 mg/kg/day	Goal: 30.4% Sub: 15% Supra: 54.6%	Goal: 33.4% Sub: 35.7% Supra: 27.4%	Goal: 33.5% Sub: 41.8% Supra: 21.2%
Loading Dose Over 2.5 Hours with Continuous Infusion Commencing 12 Hours Following Start of Loading Dose				
25 mg/kg	25 mg/kg/day	Goal: 33% Sub: 16% Supra: 51%	Goal: 38.5% Sub: 18.7% Supra: 38.8%	Goal: 37.4% Sub: 16.8% Supra: 41.9%
20 mg/kg	25 mg/kg/day	Goal: 55.7% Sub: 23.8% Supra: 20.5%	Goal: 41.4% Sub: 17.9% Supra: 36.4%	Goal: 36.1% Sub: 16.6% Supra: 43.5%
20 mg/kg	20 mg/kg/day	Goal: 58.4% Sub: 27% Supra: 14.6%	Goal: 40.7% Sub: 38.5% Supra: 16.6%	Goal: 37.9% Sub: 36.8% Supra: 21.3%

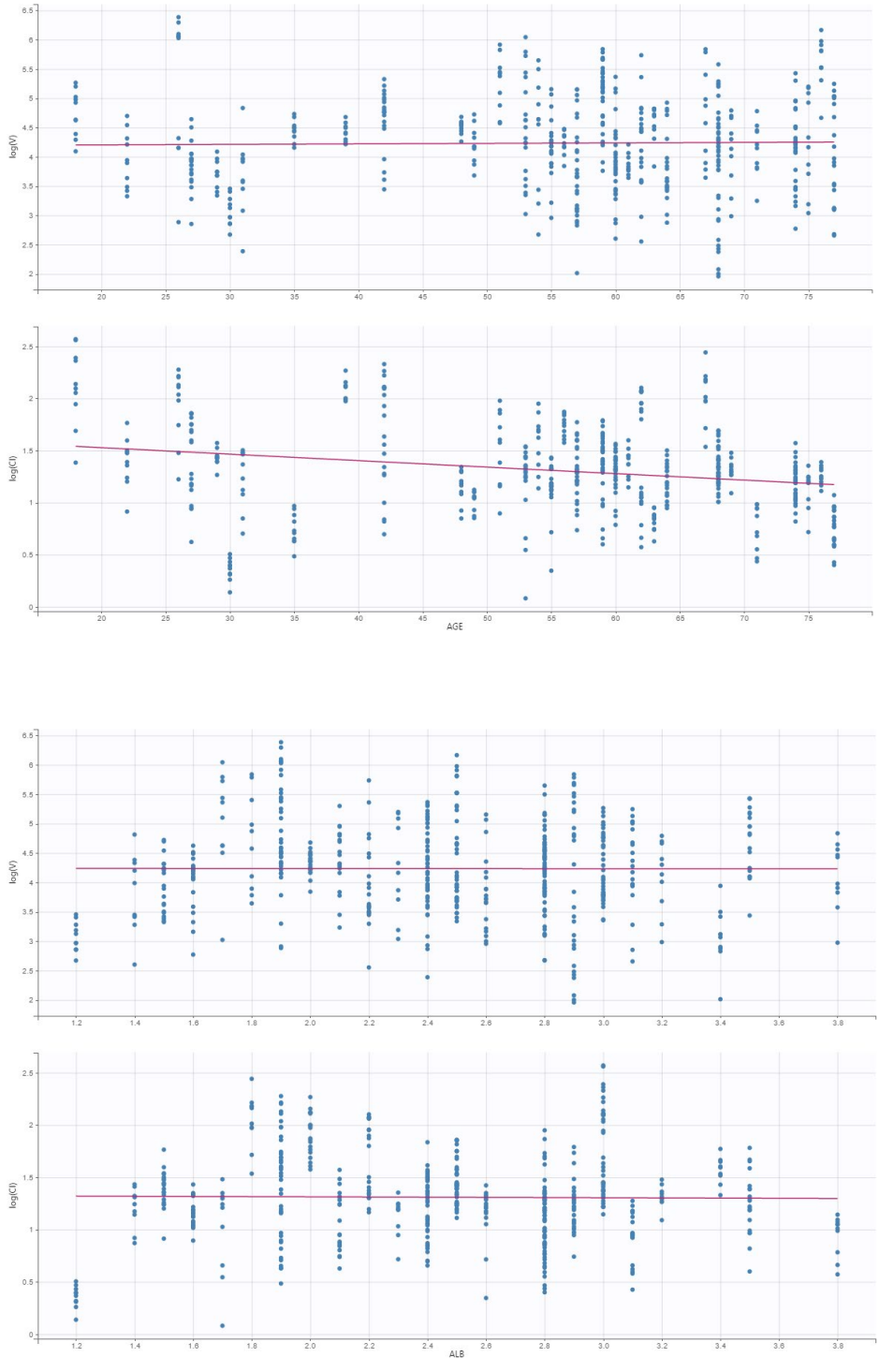
Goal= at goal range of 400-600 mg·hr/L; Sub=below 400 mg·hr/L; Supra=Higher than 600 mg·hr/L

Table 6.6 Proposed Dosing Nomogram and AUC Target Attainment

Category	Age ≤ 55			Age >55		
BUN >23	Load: 20 mg/kg Maintenance: 20 mg/kg/day			Load: 20 mg/kg Maintenance: 15 mg/kg/day		
	AUC_{0-24}	AUC_{24-48}	AUC_{48-72}	AUC_{0-24}	AUC_{24-48}	AUC_{48-72}
	Goal: 70% Sub: 10.5% Supra: 19.5%	Goal: 53.3% Sub: 26.2% Supra: 20.5%	Goal: 49.3% Sub: 25.2% Supra: 25.5%	Goal: 62.2% Sub: 3% Supra: 34.8%	Goal: 51.4% Sub: 30.8% Supra: 17.8%	Goal: 51.7% Sub: 30% Supra: 18.3%
BUN ≤ 23	Load: 20 mg/kg Maintenance: 30 mg/kg/day			Load: 20 mg/kg Maintenance: 25 mg/kg/day		
	AUC_{0-24}	AUC_{24-48}	AUC_{48-72}	AUC_{0-24}	AUC_{24-48}	AUC_{48-72}
	Goal: 60% Sub: 33% Supra: 7%	Goal: 52.5% Sub: 25.3% Supra: 22.2%	Goal: 54% Sub: 22% Supra: 24%	Goal: 71.2% Sub: 15.2% Supra: 13.6%	Goal: 57.1% Sub: 18.4% Supra: 24.5%	Goal: 51.8% Sub: 16.9% Supra: 31.3%

Simulation for patient weights 70-100 kg with maintenance dose beginning 12 hours following initiation of the loading dose.
BUN=serum blood urea nitrogen in mg/dl; Goal= at goal range of 400-600 mg·hr/L; Sub=below 400 mg·hr/L; Supra=Higher than 600 mg·hr/L

Figure 6.1 Visual Evaluation of Covariate Relationship with Parameters



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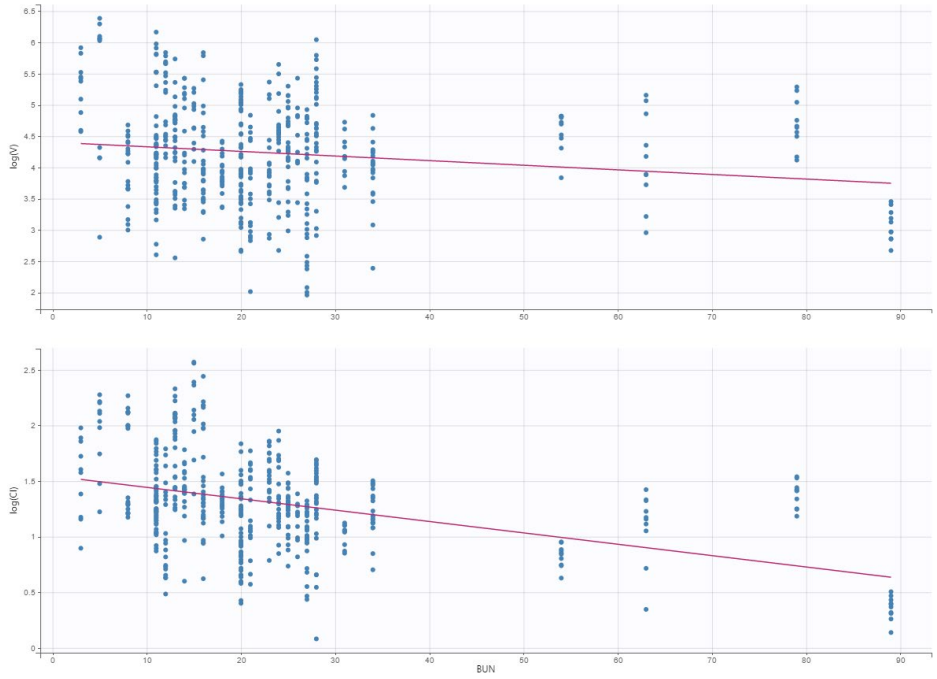

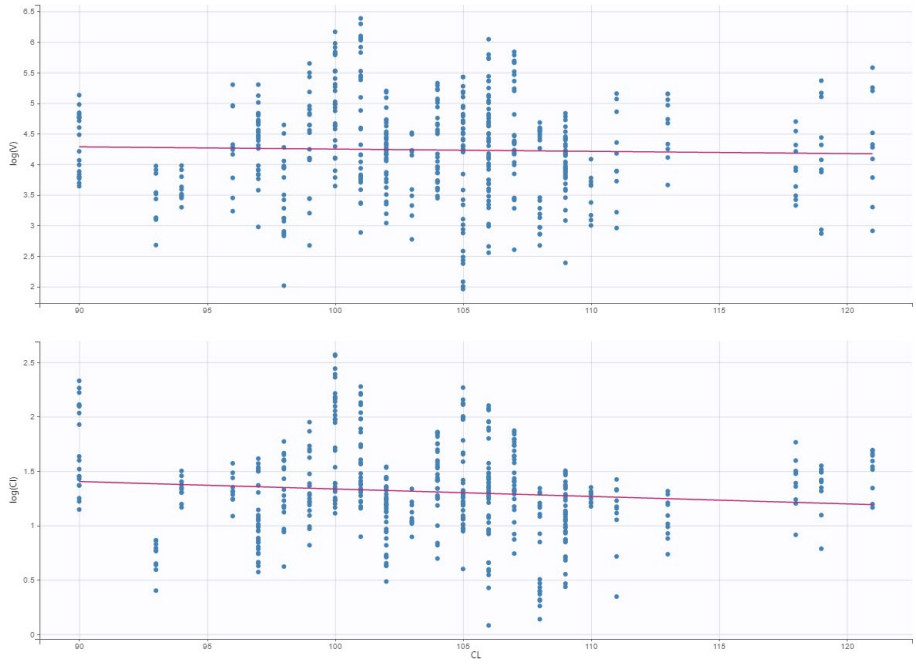

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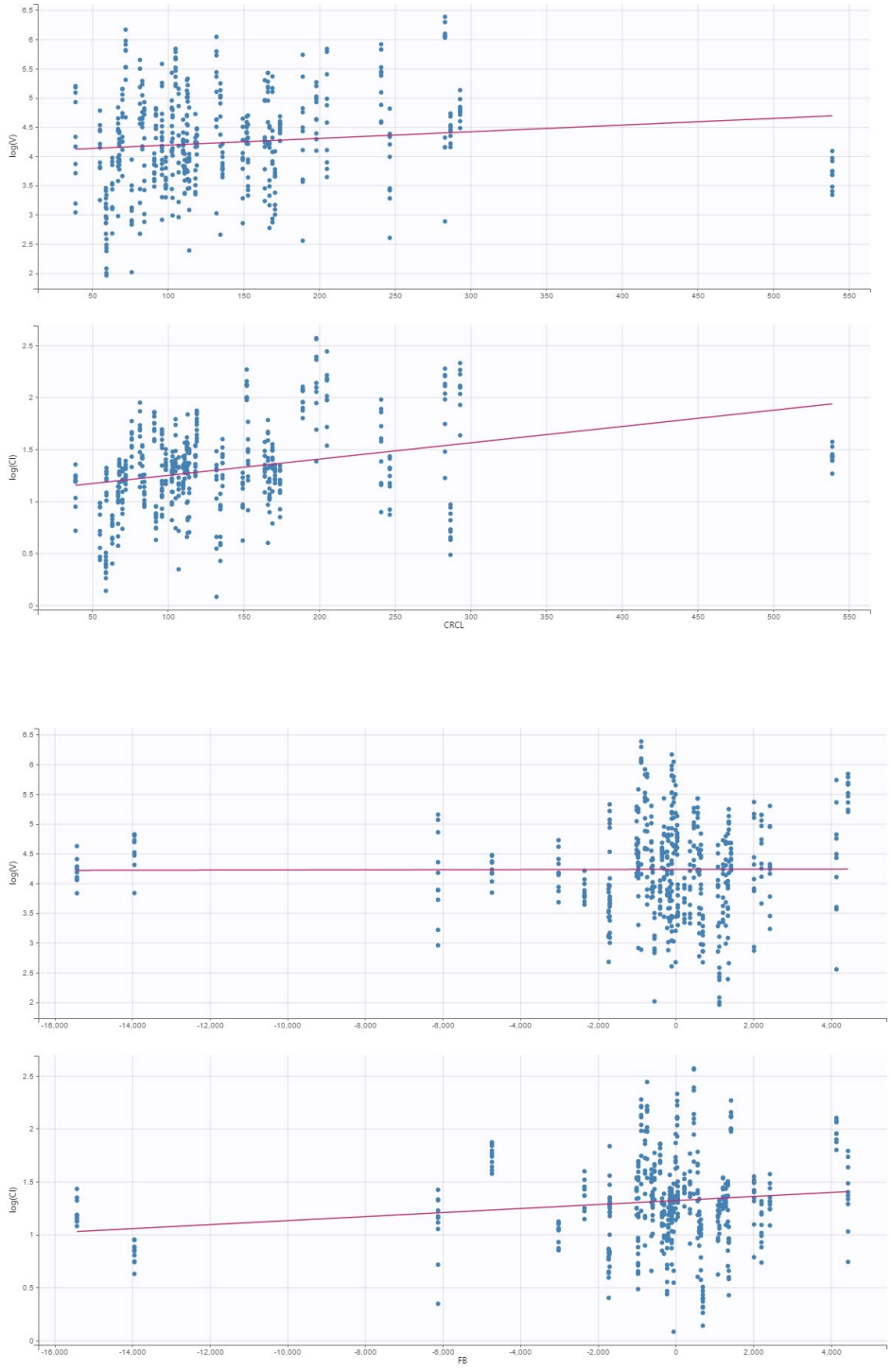

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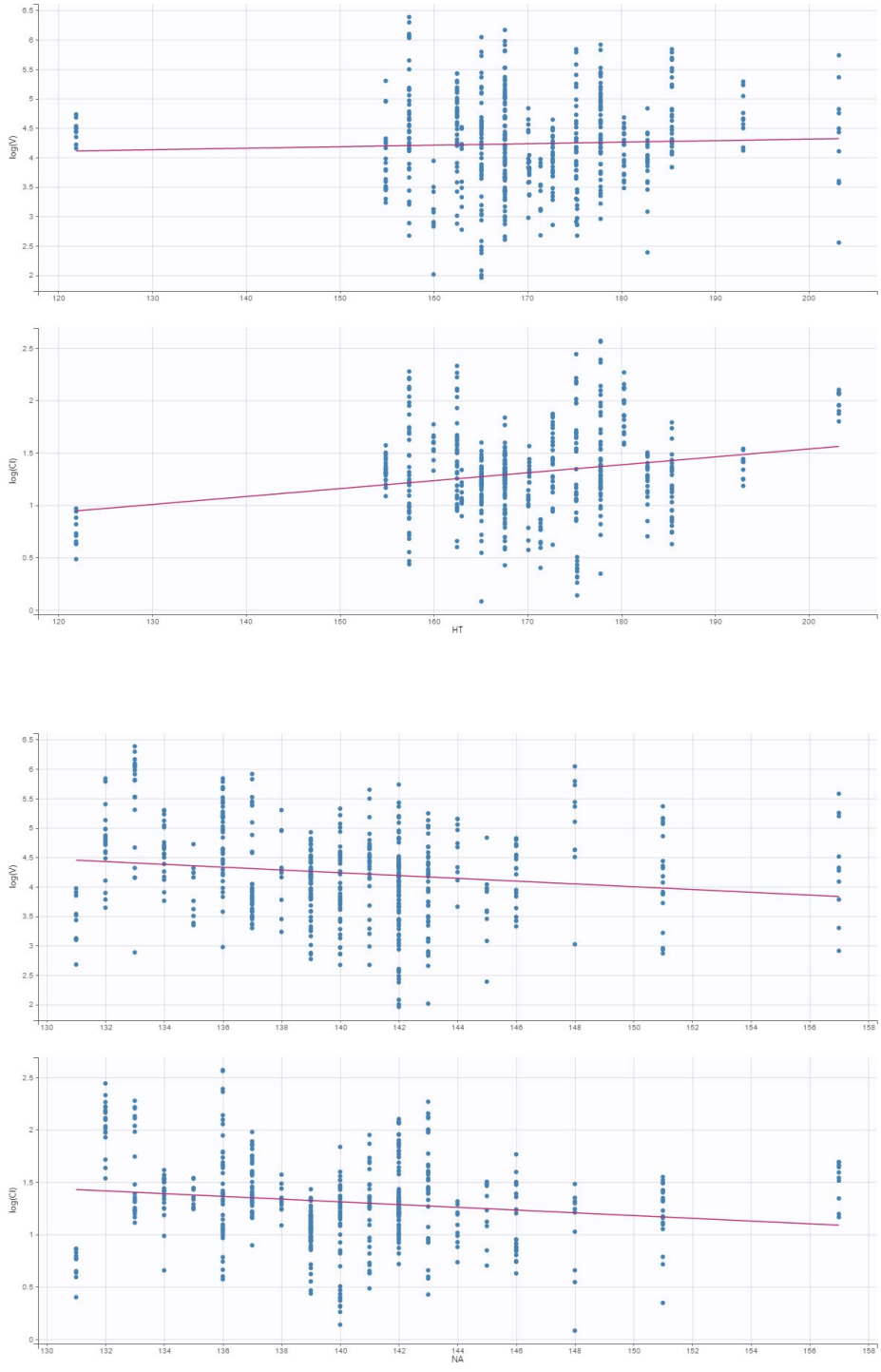

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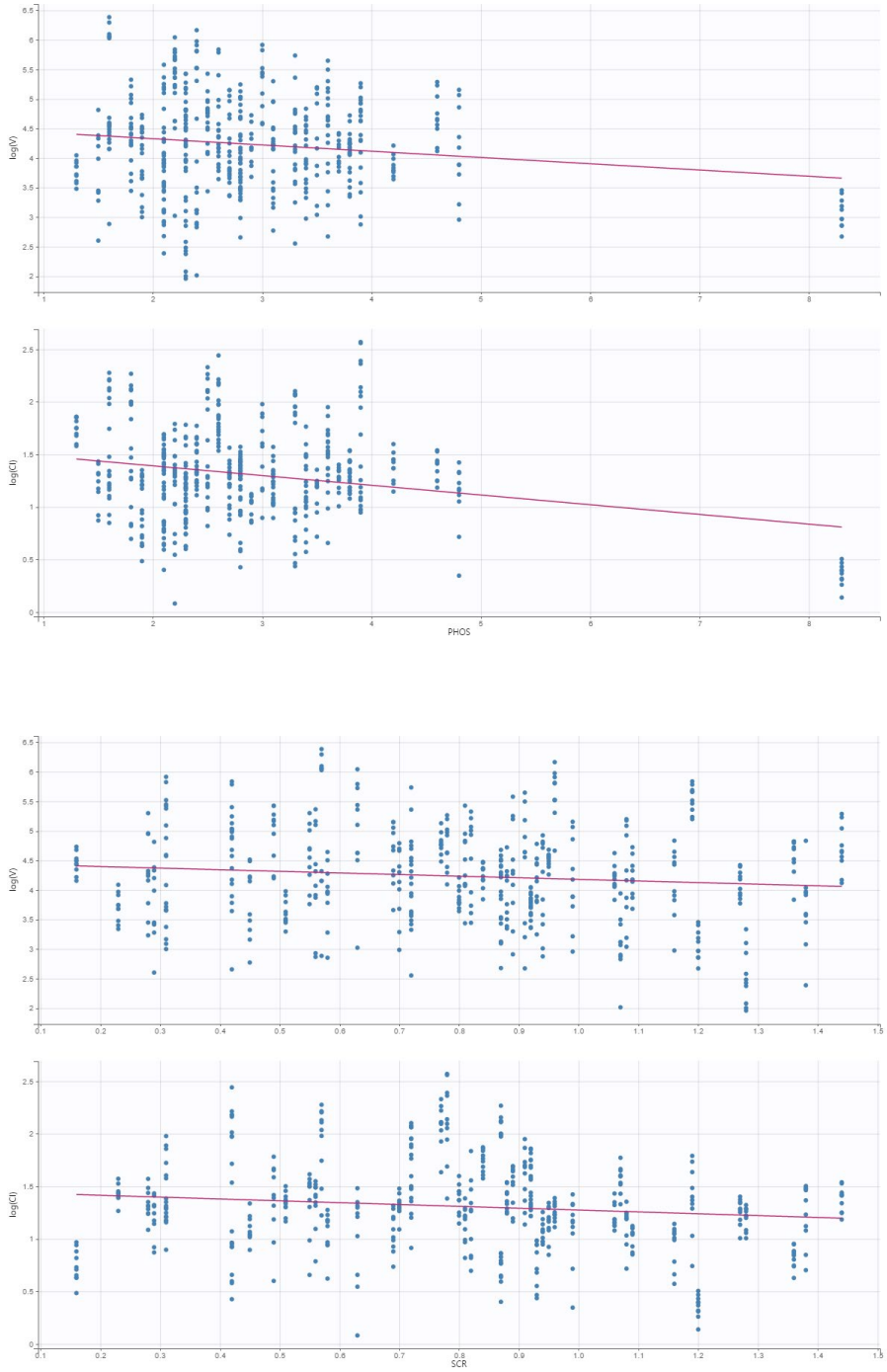

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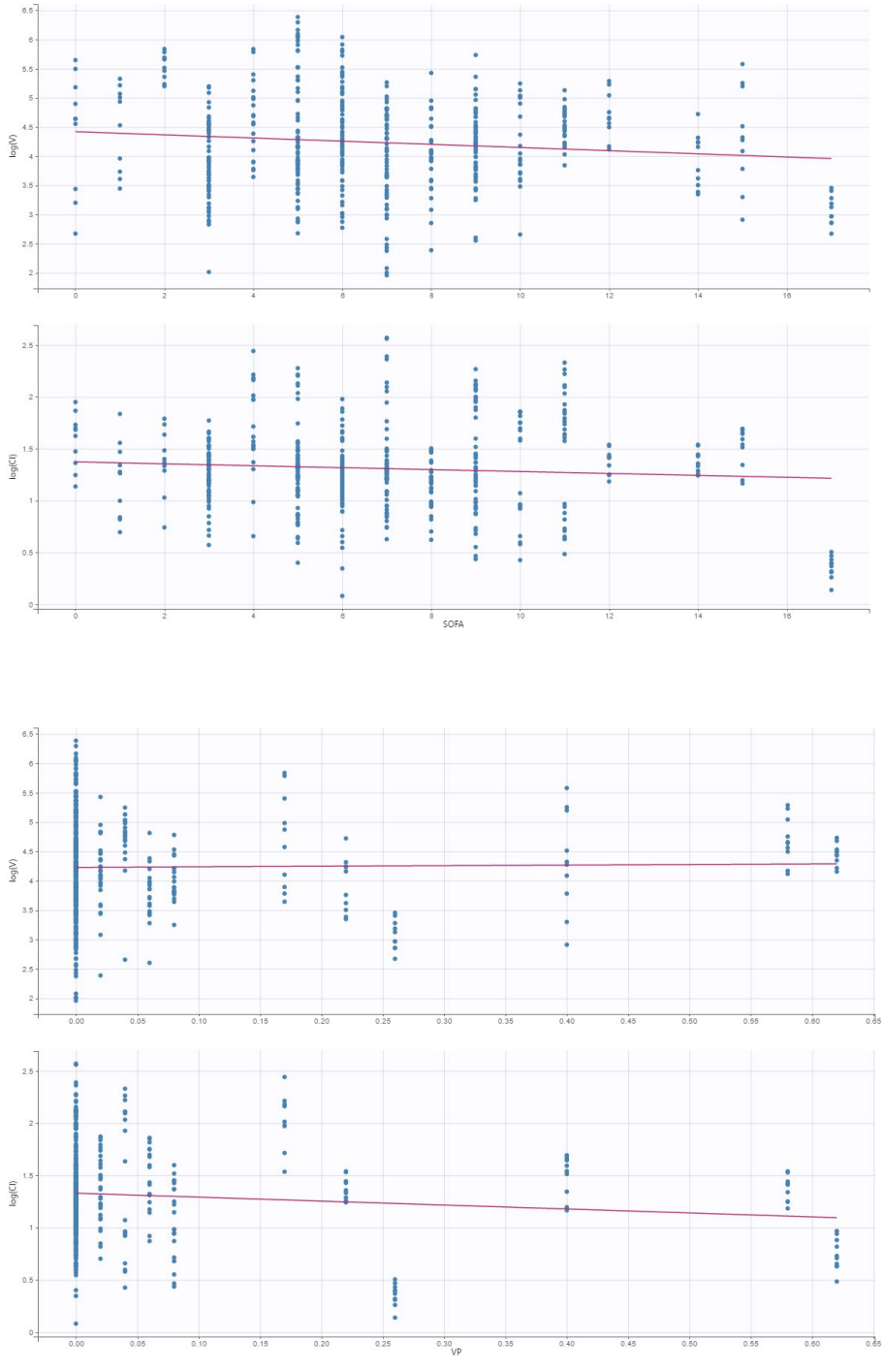

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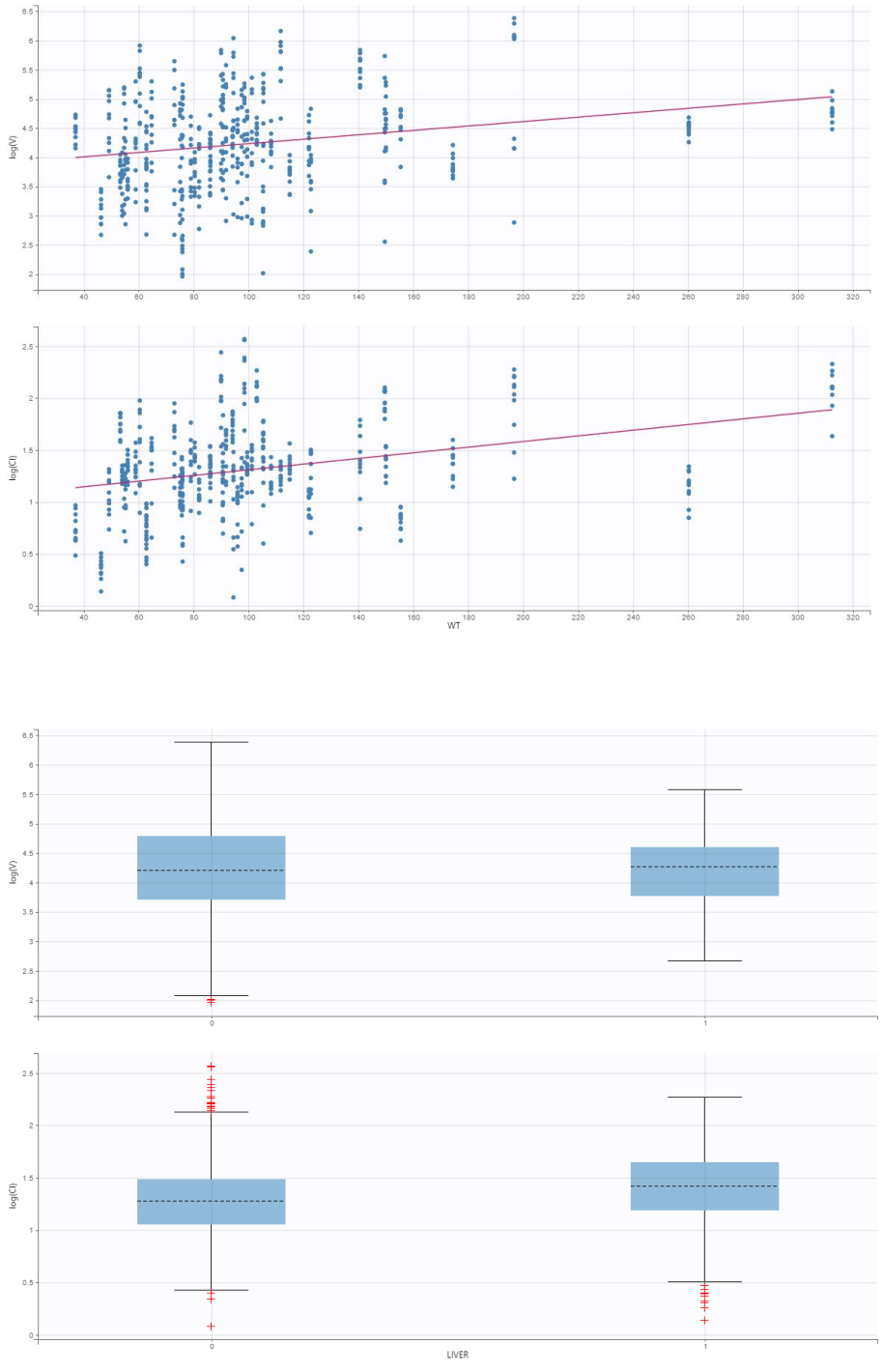

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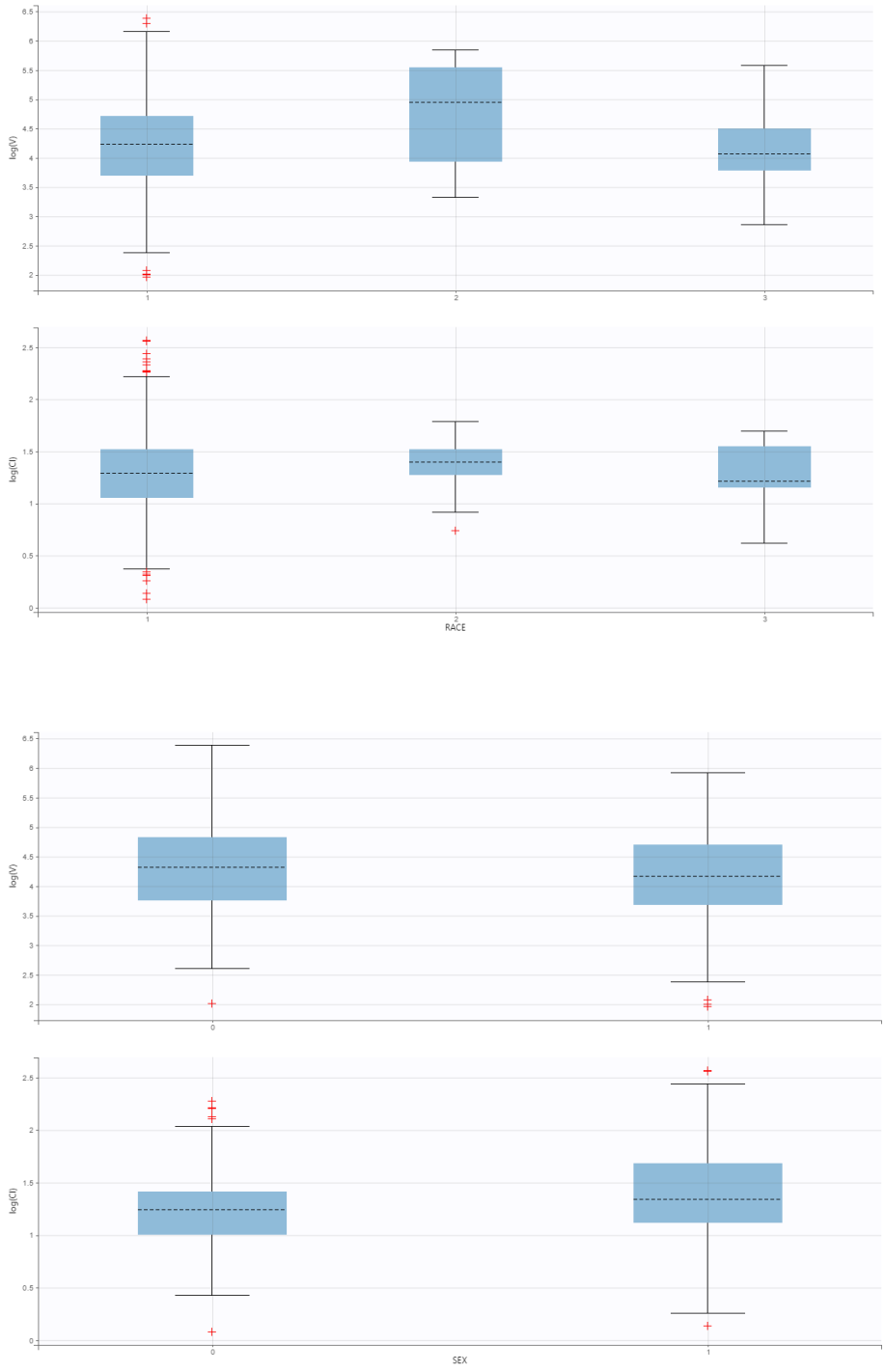


Figure 6.2 Observed Versus Predicted Population and Individual Concentrations

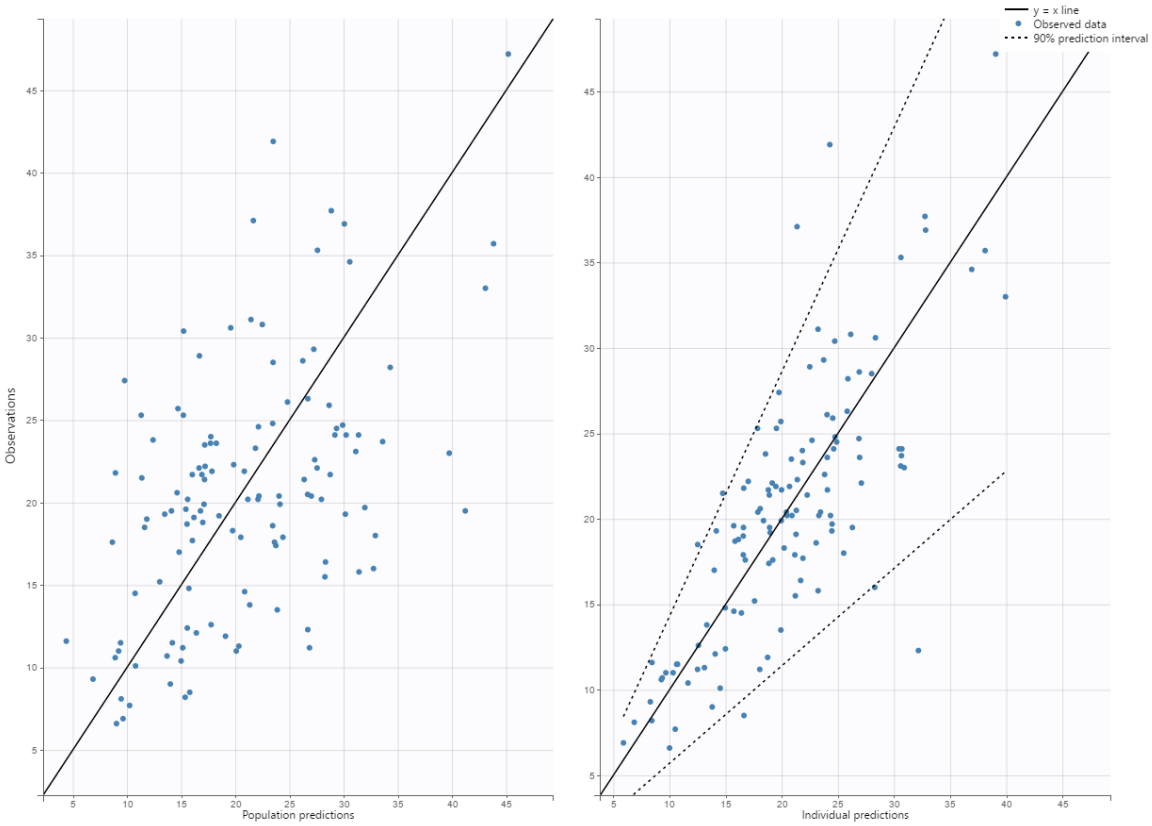


Figure 6.3 Scatter Plot of Residuals for Final Model

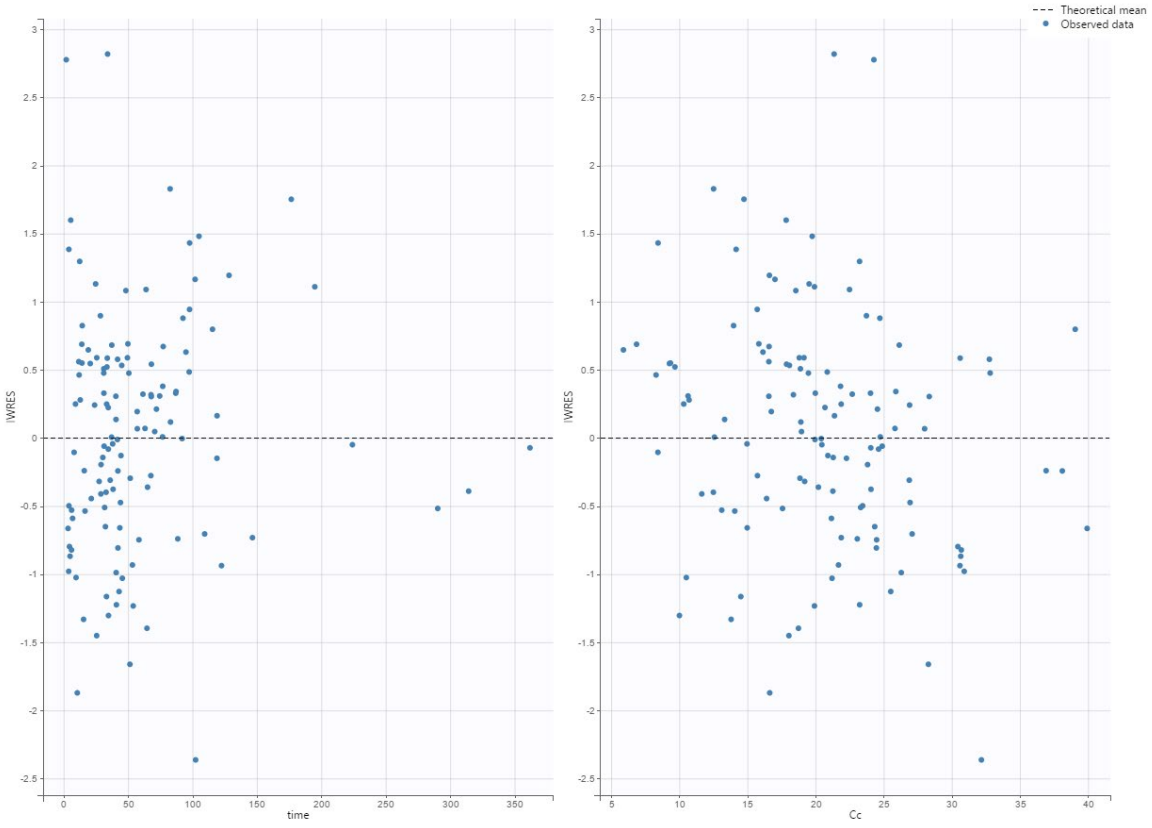


Figure 6.4 Distribution of Residuals for Final Model

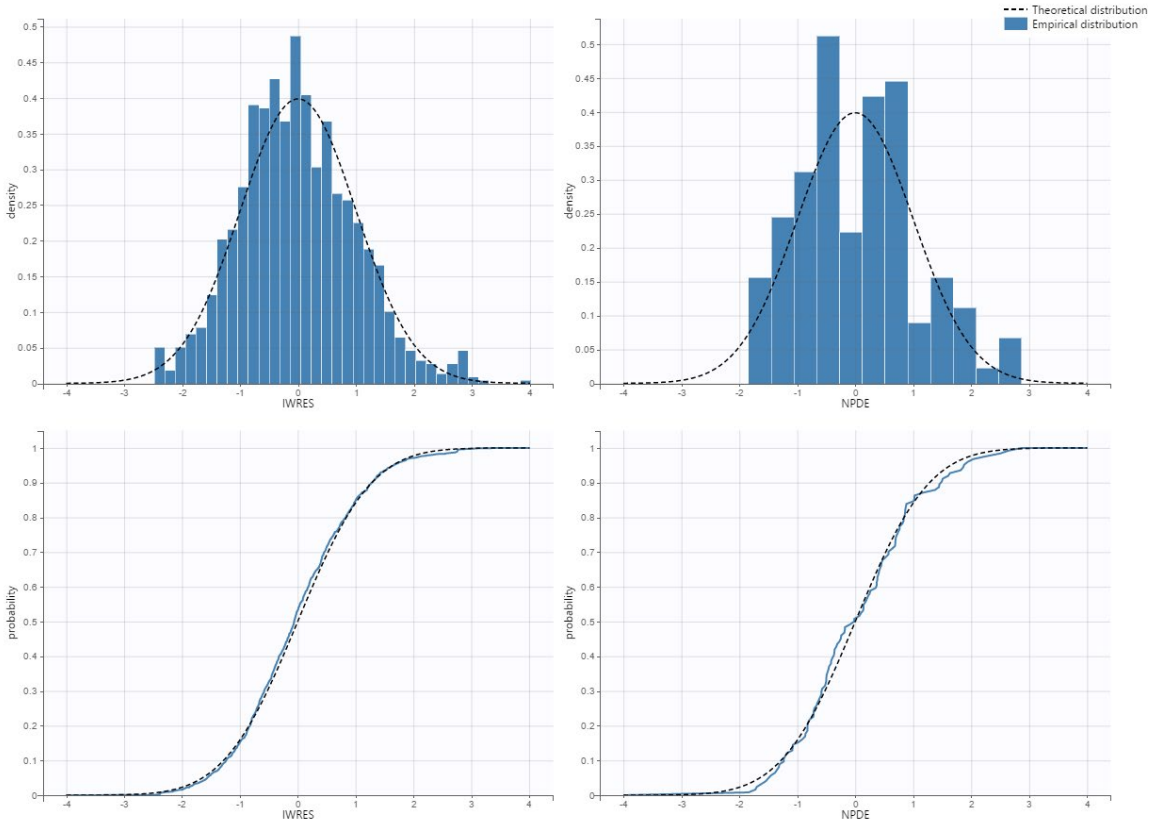


Figure 6.5 Distribution of Clearance

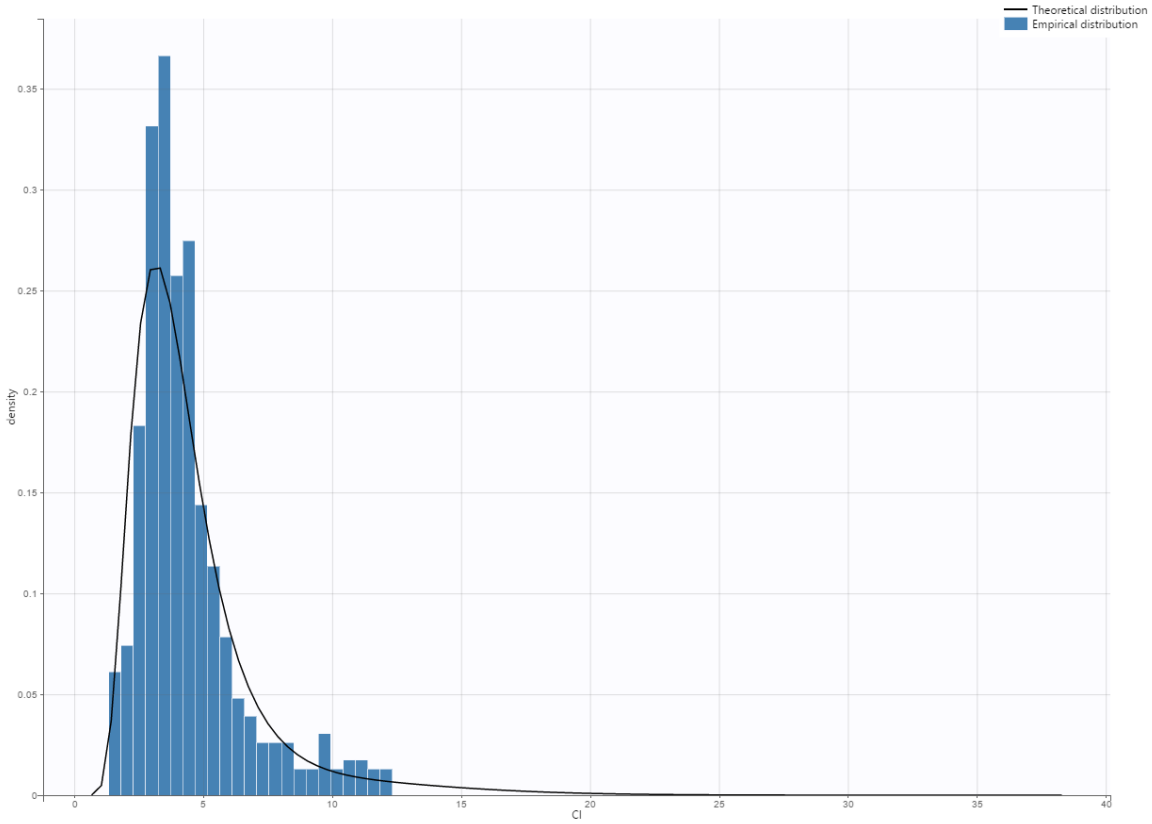


Figure 6.6 Distribution of the Standardized Random Effect for Clearance

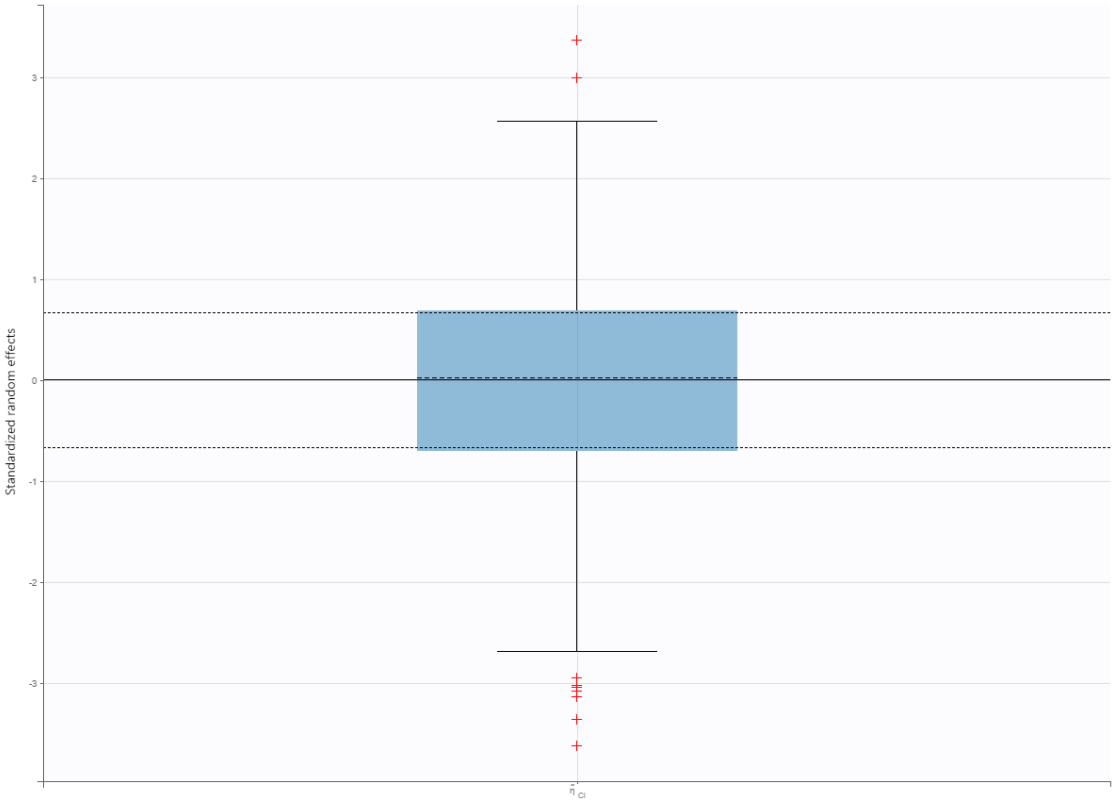


Figure 6.7 Model Convergence

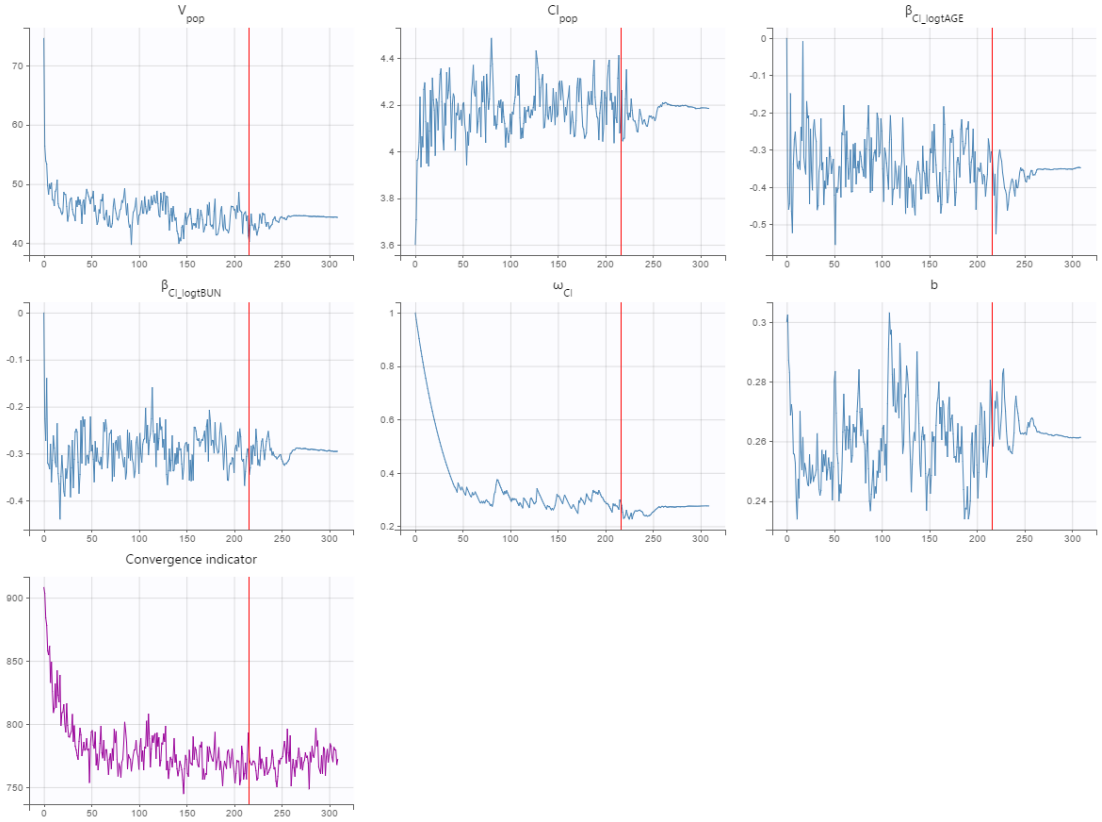


Figure 6.8 Simulation of 1000 Patients of Typical Weight (70-100kg): 25 mg/kg Loading Dose Followed by 30 mg/kg/day Continuous Infusion Starting Immediately Following Loading Dose

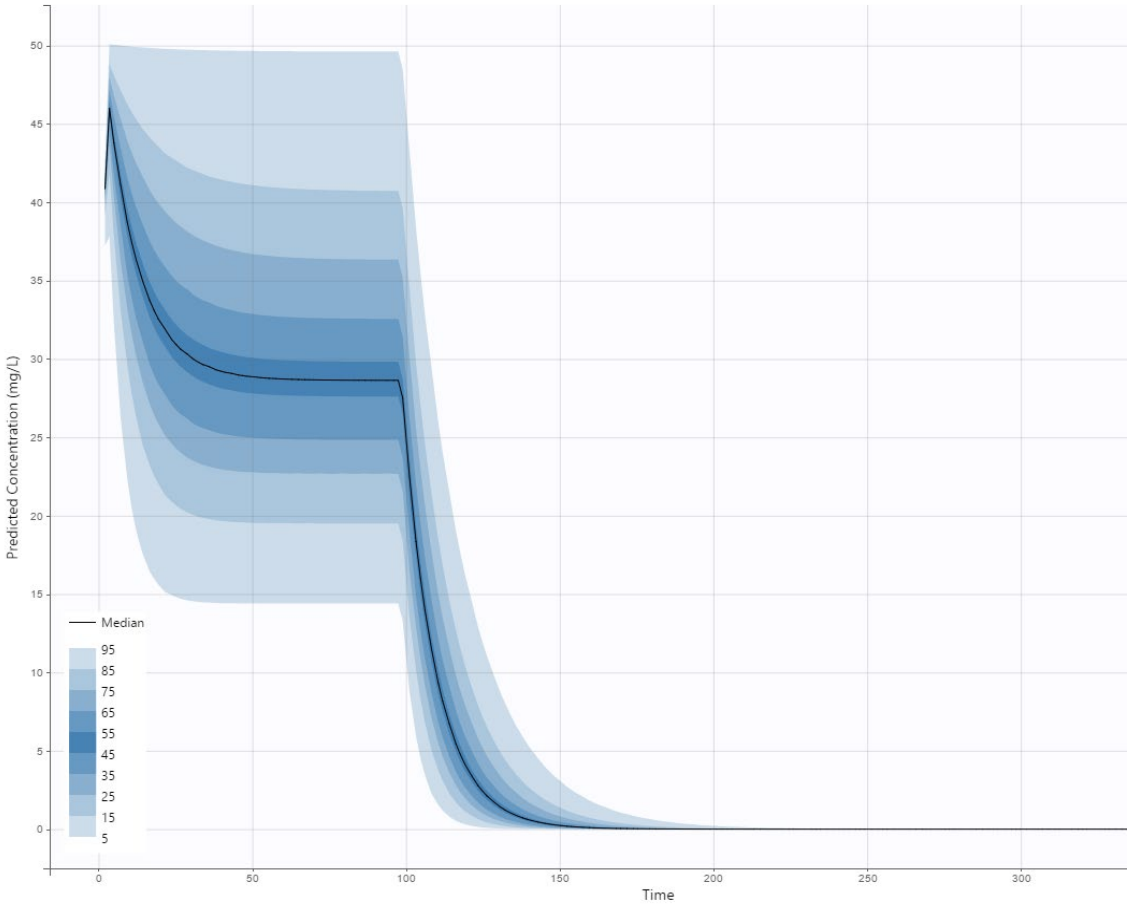


Figure 6.9 Simulation of 1000 Patients of Typical Weight (70-100 kg): 20 mg/kg Loading Dose Followed by 20 mg/kg/day Continuous Infusion Starting 12 Hours Following Start of Loading Dose

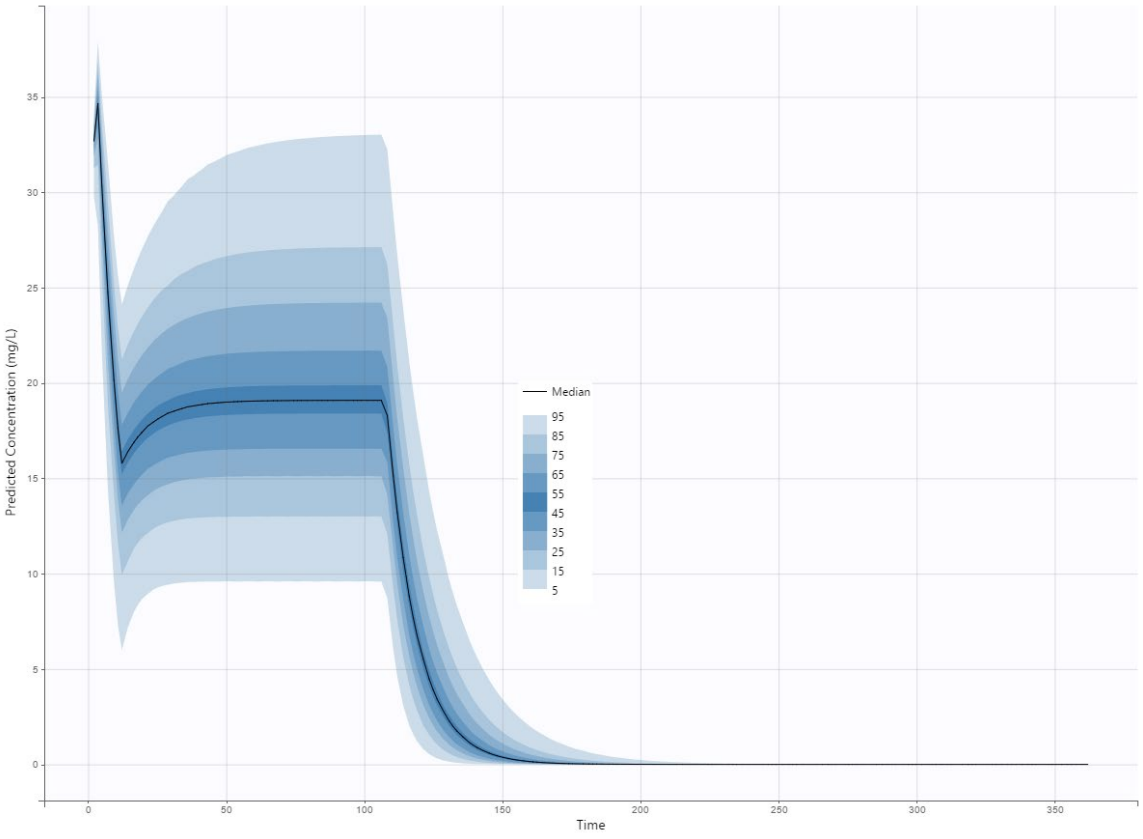
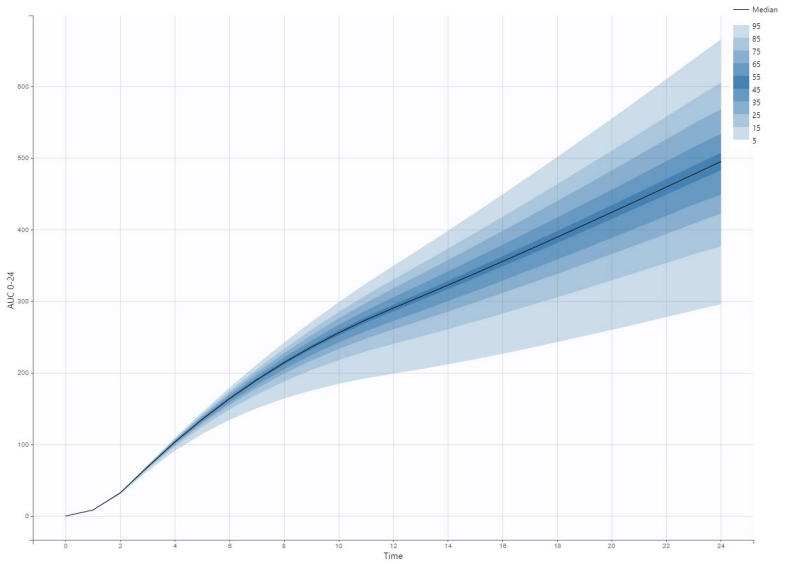


Figure 6.10 Area-Under-the-Curve Simulation of 1000 Patients of Typical Weight (70-100 kg): 20 mg/kg Loading Dose Followed by 20 mg/kg/day Continuous Infusion Starting 12 Hours Following Start of Loading Dose



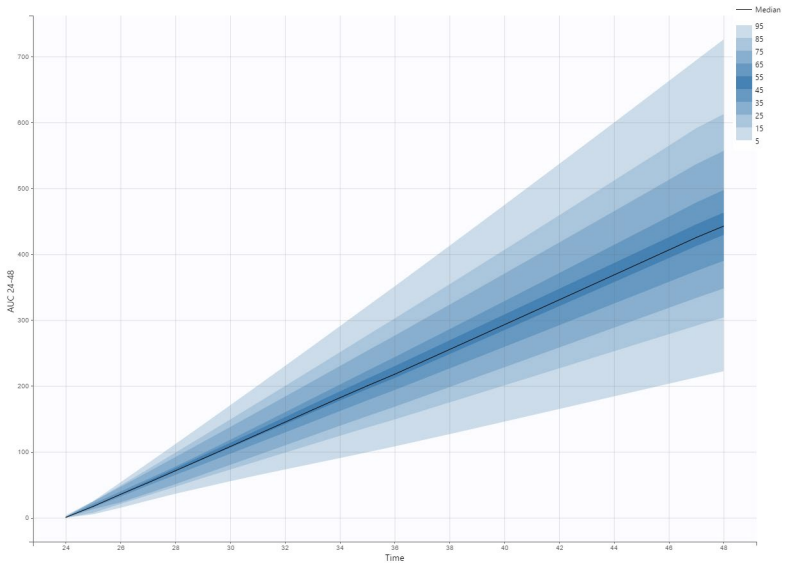
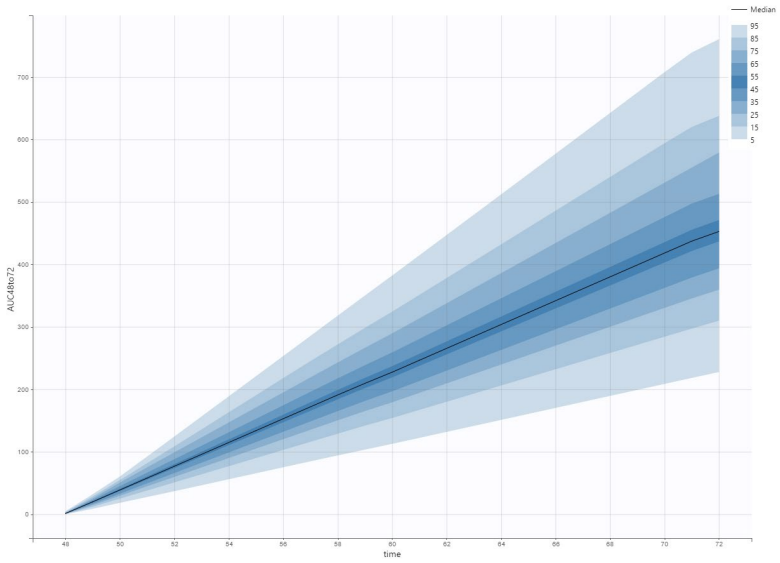


Figure 6.10 (con)



CHAPTER 7 DISCUSSION

7.1 Aim 1

Our series of studies further inform precision drug delivery of vancomycin to critically ill patients. We primarily were interested in evaluation of three techniques to optimize drug delivery of vancomycin to critically ill patients: loading doses, first-dose pharmacokinetic evaluation, and use of continuous rather than intermittent infusion. With these strategies in mind, we began our work in aim 1 by first establishing practice patterns of critical care clinicians related to vancomycin drug delivery.[75] We found that two of the drug delivery techniques that we were interested in studying were infrequently used by practicing pharmacists in adult critical care units.[75] Ninety four percent of our survey respondents either rarely or only sometimes reported first-dose pharmacokinetic evaluation to guide empiric dosing. Similarly, 98.6% of respondents reported rarely or only sometimes using continuous infusions of vancomycin.[75] If we were to demonstrate improvements in precision drug delivery with these strategies, they could have the potential to change the way vancomycin is delivered to critically ill patients throughout the world based on our international survey showing a low prevalence of these practices. We hypothesized that the frequency of loading doses would be more common given their recommendation in vancomycin consensus guidelines,[23] but still observed differential reported frequency across various scenarios.[75] Anticipating this based on a previous study of vancomycin dosing practices,[39] we sought to understand barriers for clinicians not reporting more frequent use of loading doses and incorporate these hesitations into our methods of aim 2. Indeed, a recent systematic review of implementation science research in emergency medicine emphasized the importance of understanding barriers and enablers in practice.[150]

7.2 Aim 2

These findings were important to us in designing our study assessing vancomycin loading doses in aim 2 and drove the inclusion of the primary outcome as clinical failure and ensuring assessment of the secondary outcome of acute kidney injury. Simply put, we sought to use this survey to ascertain clinician barriers to using loading doses, and then use those concerns to try and design a study to test if those concerns were valid. Our study in aim 2 of loading doses should alleviate concerns of nephrotoxicity from loading doses that some clinicians had in our survey, but also likely supports their non-universal use of a loading dose based on the lack of impact of observed clinical outcomes.[75] This highlights an important facet for further research in precision dosing of vancomycin, or any medication for that matter, in clinical care: while optimization of pharmacokinetic target attainment may be perceived to be beneficial by researchers and even guidelines, it may be insufficient to persuade clinicians to universally adopt, particularly if the action is accompanied by an increased workload, risks to the patient, or other disadvantages. Indeed, since the release of the revised vancomycin consensus guidelines recommending AUC over trough monitoring, this approach has been vigorously challenged in the literature, the outcomes justifying use of AUC over trough monitoring, and resources required to do so.[151-154] Given the link of vancomycin-associated nephrotoxicity with real, adverse clinical outcomes, including hospital readmissions and mortality and the associated healthcare costs, the counter-debate is that vancomycin AUC monitoring reduces the risk of nephrotoxicity.[155] Even with the recognition that vancomycin-induced nephrotoxicity most commonly occurs after 4-5 days of treatment,[44] the consideration that serum creatinine lags well-behind as an injury marker should give some concern

regarding the injury potentially present earlier in therapy, including sub-clinical kidney injury. Indeed, AUC monitoring may be cost-effective from the acute kidney injury perspective alone.[156] Interestingly, since completion of aim 2, another group has evaluated the efficacy of vancomycin loading doses on critically ill patients with MRSA pneumonia.[157] Although the sample size was smaller, they also observed no difference in any clinical efficacy outcomes.[157] While we believe early AUC target attainment within the initial days of therapy to still be critical from a safety perspective if nothing else, and while our work does not provide definitive answers to this topic in the manner that a randomized controlled trial would, we find it unlikely that future research on clinical outcomes related to a single, initial dose of a drug in MRSA infection would yield significant, patient-centered differences in outcomes.

7.3 Aim 3

As an early adopter of the transition to AUC-guided vancomycin dosing, our team had clinical experience with vancomycin AUC dosing. Our anecdotal experience was that traditional nomograms, or even clinical judgement used to guide empiric dosing of vancomycin, was producing wide-ranging AUCs, very few of which were in the target range. In aim 3, we confirmed this suspicion where we found that empiric dosing of vancomycin in critically ill medical ICU patients achieved AUC target attainment at steady state only 32.4% of the time.[149] By using a first-dose pharmacokinetic approach in patients with stable renal function, whereby 2 vancomycin concentrations were assessed following the first dose to calculate patient-specific pharmacokinetic parameters, we demonstrated this approach nearly doubled AUC target attainment at steady state to 58.6%.[149] The advantages of this approach are relatively clear: using patient-specific

dosing information assures more precise dosing and less likely to see variability in AUC. If the patient has confirmed MRSA, this is advantageous to ensure appropriate AUC/MIC attainment. If the therapy is empiric, this ensures the patient does not experience unnecessary and risky extremes of vancomycin exposures given vancomycin's nephrotoxicity risk, particularly in critically ill patients with multiple kidney insults present at any given time. The challenge to precision dosing of any medication, including vancomycin, is that increasing precision will come with added cost of care. In the case of Bayesian software programs, the cost is more tangible, direct, and known up-front, which has been documented to hinder their use in practice.[158] While this first-dose pharmacokinetic approach does not carry those same costs, it does come with costs of additional vancomycin concentrations and clinician effort to appropriately use the information gained from very early concentration assessment. We suspect that clinicians with a prior belief that early AUC target attainment is clinically relevant for efficacy and safety outcomes will be attracted by this approach, while skeptical clinicians with low prior beliefs about the value of early AUC target attainment are less likely to implement. Since even the Bayesian methods rely heavily on the population pharmacokinetic models incorporated and produce more accurate predictions once a patient's own vancomycin concentration has been incorporated into the Bayesian forecasting,[159,160] one possible expansion of this research in the future may include the assessment of a single vancomycin concentration following the initial dose to better inform precise dosing of vancomycin.

Using the first-order pharmacokinetic equations in clinical practice in the same method that they are applied to pharmacokinetic studies is often challenging. Medication

doses are often not administered at the exact time intervals, concentrations are not always drawn at precise times, and other logistical issues. As our center instituted AUC monitoring and developed the protocol for first-order pharmacokinetic equations, one gains an appreciation of the sheer amount of inherent potential error in this math. Variability occurs in not only the measurement of the vancomycin concentration from the laboratory, but also assumptions about the occurrence of steady state, that levels are obtained one half-life apart, back- and forward- extrapolations for concentrations that are drawn late or early, respectively. Our interest in continuous infusions of vancomycin was based not only on the ease of clinical use and relaxing some of the assumptions and resources required to monitor (one concentration required for AUC assessment versus two), but also due to an interest that continuous infusions of vancomycin may reduce the risk of acute kidney injury.

7.4 Aim 4

As we noted in aim 4, our meta-analysis was unique in that it focused on critically ill patients and used appropriate statistical techniques to account for the adjusted effect estimates produced from some of the included studies. For example, pooling results from critically ill patients and patients receiving home infusions of vancomycin is analogous to pooling apples and oranges, a common critique of meta-analytic approaches in general. The authors of prior cohort studies took care to adjust for confounding in their presentation of the results, and it seems appropriate that these adjusted estimates (i.e. with confounding minimized) would be appropriate to pool rather than unadjusted estimates from non-randomized studies. In the meta-analysis of aim 4, we found that continuous vancomycin infusions in critically ill patients were associated with more than a 50%

reduction in the odds of acute kidney injury.[70] As we continue to plan for future studies comparing continuous versus intermittent infusion of vancomycin and kidney injury, this estimate can help us derive a planned effect size for sample size calculations.

Similar effects of continuous versus intermittent infusion have been observed in pre-clinical models as well. Supporting this concept of peak vancomycin concentrations being a driver of kidney injury, rats were given equivalent daily doses fractionated over various dosing intervals, including once, twice, three, or four times daily.[46] Urinary kidney injury molecule-1 (KIM-1) was approximately tripled in the once and twice daily groups compared to the three and four times daily groups. In the same model, vancomycin AUC and C_{max} were both moderately or strongly correlated with urinary KIM-1 and osteopontin.[6] KIM-1 is a proximal tubule injury marker that has previously been shown to correlate with histopathologic damage of the proximal tubules in vancomycin induced kidney injury.[121] Our group has studied KIM-1 in clinical AKI studies and shown that in critically ill patients with AKI, urinary KIM-1 is approximately two-fold higher 24-48 hours following AKI compared to critically ill patients without AKI with measures at ICU admission.[161] We have also shown that KIM-1 is associated with the composite outcome of major adverse kidney events (death, renal replacement therapy, or reduced kidney function) out to six months.[161] This knowledge of KIM-1's behavior in clinically relevant AKI will also be useful in designing future studies incorporating urinary biomarkers of kidney injury between patients treated with continuous versus intermittent infusion.

In our systematic review and meta-analysis conducted in aim 4, one interesting theme that appeared to emerge is that while intermittent dosing of vancomycin was

typically carefully planned with nomograms, continuous infusions of vancomycin were often based on a flat dose of 30 mg/kg/day.[70] This discrepancy in careful, deliberate dosing for one dosing strategy compared to a one-sized fits all approach for another strategy appeared to be at odds with evaluation of precise vancomycin dosing. To our knowledge, no cross-over study evaluating the clearance of vancomycin when administered continuously versus intermittently has been completed, thus while we assume that clearance is equivalent between the two dosing strategies based on principles of first-order elimination, the kidneys may handle vancomycin differently depending on the infusion strategy. Before we embark on future comparisons of continuous versus intermittent infusions of vancomycin, it seemed necessary to develop dosing schemes of continuous infusion vancomycin with the same level of effort that has been put into developing dosing schemes of intermittent infusion of vancomycin.

7.5 Aim 5

In order to accomplish this, in aim 5 we studied 50 patients from the medical intensive care unit with 124 associated vancomycin serum concentrations and used dosing information obtained from clinical care to develop a population pharmacokinetic model for continuous infusion of vancomycin in this patient population. We successfully developed a one-compartment model to fit the data, parameterized by vancomycin clearance and volume. We observed significant covariate effects of BUN, weight, and age on vancomycin clearance that improved the fit of the model to the data, and compared and contrasted our model to others published using continuous infusion vancomycin in Chapter 6. We also derived important insights on the dosing of continuous infusion vancomycin from our simulations, including a simplified nomogram for the

maintenance dose and useful information on how the time interval from loading dose to maintenance dose initiation impacts the AUC during this time period. Our finding that delaying the initiation of the continuous infusion to 12 hours following the start of the loading dose is not only highly clinically relevant as outlined in Chapter 6, but it is also extremely useful for the design of future clinical studies testing continuous versus intermittent infusion. If the continuous infusion was required to be initiated shortly following the loading dose to not delay care, this would have made the design of a comparative effectiveness trial quite difficult given the short time interval for informed consent. However, by having this 12-hour window between the start of the next dose, when administered continuously or intermittently, the logistics of informed consent for such a trial become much more feasible.

7.6 Strengths and Limitations

When considered in totality, the five aims presented have considerable strengths, particularly their granular considerations of vancomycin doses and concentrations, sufficiently powered considering each study's objective, and rapid ability to translate to clinical practice should a clinician or institution wish to adopt the particular strategies studied for precision dosing of vancomycin. While survey techniques and meta-analytic techniques have their own limitations, the primary limitation from our clinical data, particularly the pharmacokinetic data obtained in aims 3 and 5, is that they are derived from a single ICU in a single medical center. Other ICU populations may carry unique nuances, such as a higher incidence of augmented renal clearance or other pharmacokinetic alterations, compared with the medical ICU which is primarily a septic and respiratory failure population. Kentucky is over 85% white,[162] and also one of the top

10 states in the country regarding obesity,[163] which in concert with the single center nature may limit generalizability of these findings to other critically ill patients.

7.7 Future Directions

Critically ill patients have always represented a unique challenge for drugs with narrow therapeutic indices not only due to the presence of pharmacokinetic changes, but also the fluctuations that can occur in these patients from day-to-day that may influence pharmacokinetics. While we did not employ Bayesian forecasting in our aims, our data from aim 5 and the population pharmacokinetic model we have built serves as preliminary data to serve as priors in future Bayesian models for continuous infusions of vancomycin. For a more simplified approach, our simplified dosing nomogram developed also awaits further validation. While our data from aim 3 demonstrate that an intensive pharmacokinetic monitoring strategy following the first dose can improve AUC target attainment at steady state, we anticipate this approach certainly not applicable to every patient that receives vancomycin and the laborious nature may preclude adoption by many centers. In the future, if we are able to incorporate our model into a Bayesian forecasting system, potentially a single level following the initial dose will allow us to maximize precision dosing of continuous infusion vancomycin in critically ill patients. A number of other advancements on this front may also allow us to refine dosing predictions. First, serum creatinine is well-recognized as a poor predictor of renal function for dosing and assessing AKI, and this was confirmed in our population pharmacokinetic model where creatine clearance was poorly correlated with estimated parameters. Serum cystatin C has been shown to predict vancomycin troughs better than serum creatinine,[164] and using this biomarker may allow better refinement of precision

dosing estimates based on current renal function. Second, real-time glomerular filtration rate (GFR) assessment using fluorescent molecules allows for continuous monitoring of GFR which not only has implications for early detection of AKI, but also for potential to incorporate into precision dosing strategies.[165] Microsampling techniques are also being developed that would minimize the invasiveness and labor associated with blood draws during therapeutic drug monitoring, which may allow for more frequent monitoring of vancomycin levels. In addition to the typical challenges of developing these technologies such as blood-plasma correlation, they need to be validated in critically ill patients specifically given shunted blood flow.[166]

While vancomycin stewardship is undoubtedly an important area of clinical focus to reduce unnecessary vancomycin exposure, our ability to optimize dosing for those who need it, particularly early in therapy, as well as protect the most vulnerable patients from further, significant kidney insults, demands that we optimize not only the dose and exposure, but the method of administration of vancomycin to minimize harm and promote efficacy.

APPENDICES

APPENDIX 1. Vancomycin Dosing Practices Survey

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Vancomycin Dosing Practices Among Critical Care Pharmacists

Please answer the following questions regarding your personal and institutional practices regarding vancomycin involving the ICU patient population that you care for most often.

Physical Characteristics of Practice Site

Which of the following best describes the geographic location of your practice INSTITUTION?

- ◯ Midwest United States (IA, IN, IL, KS, MI, MN, MO, ND, NE, OH, SD, WI)
- ◯ Northeast United States (CT, MA, ME, NH, NJ, NY, PA, RI, VT)
- ◯ South United States (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)
- ◯ West United States (AK, AZ, CA, CO, HI, ID, NM, MT, NV, OR, UT, WA, WY)
- ◯ North America (non-United States)
- ◯ South America
- ◯ Europe
- ◯ Asia
- ◯ Africa
- ◯ Australia
- ◯ Antarctica

Which of the following best describes the type of INSTITUTION in which you practice?

- ◯ Academic medical center / rural
- ◯ Academic medical center / urban
- ◯ Community hospital / teaching / rural
- ◯ Community hospital / teaching / urban
- ◯ Community hospital / non-teaching / rural
- ◯ Community hospital / non-teaching / urban
- ◯ Government center / urban
- ◯ Government center / rural
- ◯ Other

What is the size of your INSTITUTION?

- ◯ < 250 beds
- ◯ 250-499 beds
- ◯ 500-750 beds
- ◯ >750 beds

Which of the following best describes your current level of training or clinical experience?

- ◯ Current PGY1 pharmacy resident
- ◯ Current PGY2 specialty pharmacy resident (any specialty)
- ◯ Current pharmacy fellow (any specialty)
- ◯ Practitioner < 5 years out from terminal training
- ◯ Practitioner 5-10 years out from terminal training
- ◯ Practitioner > 10 years out from terminal training

Clinical Coverage Characteristics of Practice Site

APPENDIX 1 (con)

Confidential

For which hospital location or service do you provide the majority of your patient care (i.e., primary practice ICU)?	◯ Burn ICU ◯ Cardiothoracic ICU ◯ Coronary Care Unit ◯ Emergency Department ◯ Medical ICU ◯ Mixed Medical/Surgical ICU ◯ Neurosciences/Neurosurgical ICU ◯ Surgical/Trauma ICU ◯ Other (please explain)
For which hospital location or service do you provide the majority of your patient care (other):	_____
Do pharmacists in your PRIMARY PRACTICE ICU physically round with the primary or intensivist team at least 5 days per week?	◯ Yes ◯ No
In your PRIMARY PRACTICE ICU, what percentage of Staphylococcus aureus isolates are resistant to methicillin (i.e., MRSA)?	◯ < 20% ◯ 20-39% ◯ 40-59% ◯ 60-80% ◯ > 80% ◯ Unknown/my primary practice ICU does not have a unit-specific antibiogram
How often do you estimate that vancomycin is included as empiric therapy for treatment of suspected hospital-acquired infections in your PRIMARY PRACTICE ICU?	◯ Rarely (< 10% of the time) ◯ Sometimes (10-50% of the time) ◯ Often (51-90% of the time) ◯ Routinely (> 90% of the time)
If your INSTITUTION uses a formal consult to order vancomycin (e.g., a "pharmacy to dose" order or other formal consult in the permanent medical record), which of the following options best describes your INSTITUTION's protocol and your own individual dose practices?	◯ Pharmacists must adhere to the protocol as written and may not deviate ◯ Pharmacists may deviate from the protocol as written, but I rarely do (< 10% of the time) ◯ Pharmacists may deviate from the protocol as written, which I sometimes do (10-50% of the time) ◯ Pharmacists may deviate from the protocol as written, which I often do (51-90% of the time) ◯ Pharmacists may deviate from the protocol as written, and I routinely do (> 90% of the time) ◯ No formal protocol exists in my primary practice ICU
Via a protocol or other mechanism, pharmacists at my INSTITUTION are given authority to order (choose all that apply):	☐ Vancomycin levels ☐ Laboratory tests for monitoring (e.g., basic metabolic panel) ☐ Dose adjustments based on vancomycin levels or renal function changes ☐ No protocol or other mechanism exists at my institution; orders must be placed under another provider's name via verbal/written order
In your PRIMARY PRACTICE ICU, what would you estimate is the average duration of vancomycin use prior to de-escalation when MRSA is not cultured?	◯ < 2 days (< 48 hours) ◯ 2-3 days (48-72 hours) ◯ 3-4 days (72-96 hours) ◯ > 4 days (> 96 hours)
Does your INSTITUTION report vancomycin minimum inhibitory concentrations (MICs) for MRSA in the permanent medical record?	◯ Yes ◯ No

APPENDIX 1 (con)

Confidential

Does your INSTITUTION have a protocol for dosing vancomycin in continuous renal replacement therapy (CRRT)?

- ○ Yes; but there is no mechanism to alert the pharmacist that CRRT is being initiated or discontinued
- ○ Yes; and there is a mechanism to alert the pharmacist that CRRT is being initiated or discontinued
- ○ No; and there is no mechanism to alert the pharmacist the CRRT is being initiated or discontinued
- ○ No; but there is a mechanism to alert the pharmacist that CRRT is being initiated or discontinued
- ○ My primary practice ICU does not utilize CRRT

Does your INSTITUTION have a protocol for dosing vancomycin in sustained low-efficiency dialysis (SLED)?

- ○ Yes; but there is no mechanism to alert the pharmacist that SLED is being initiated or discontinued
- ○ Yes; and there is a mechanism to alert the pharmacist that SLED is being initiated or discontinued
- ○ No; and there is no mechanism to alert the pharmacist that SLED is being initiated or discontinued
- ○ No; but there is a mechanism to alert the pharmacist that SLED is being initiated or discontinued
- ○ My primary practice ICU does not utilize SLED

Which of the following vancomycin monitoring and quality assurance programs does your current INSTITUTION offer? (select all that apply)

- ☐ Quality assurance for percentage of vancomycin dosing regimens within goal target parameters (trough or AUC)
- ☐ Real-time clinical decision support to notify pharmacists of acute changes in serum creatinine or urine output
- ☐ Standardized definition of vancomycin-associated nephrotoxocity
- ☐ None of these
- ☐ I do not know

Individual Vancomycin Dosing Strategy

For each of the following clinical diagnoses, please select how often you would recommend a loading dose (at least 25 mg per kg) of vancomycin.

	Rarely (< 10% of the time)	Sometimes (10-50% of the time)	Often (51-90% of the time)	Routinely (> 90% of the time)
Infective endocarditis	○	○	○	○
Meningitis/CNS infection	○	○	○	○
Pneumonia in a mechanically ventilated patient	○	○	○	○
Pneumonia in a non-mechanically ventilated patient	○	○	○	○

APPENDIX 1 (con)

Sepsis with shock	○	○	○	○
Sepsis without shock	○	○	○	○

When you do not choose to administer a loading dose, what are your reasons? (select all that apply)

- ☐ Lack of clinical outcome data supporting strategy
- ☐ Nephrotoxicity concerns
- ☐ Time required to infuse
- ☐ The patient does not meet my definition of severely ill
- ☐ Other (please explain)
- ☐ I always administer a loading dose

When you do not choose to administer a loading dose, what are your reasons (other)?

_____

When dosing vancomycin, which weight do you most commonly use in each of the following scenarios?

	Actual body weight	Ideal body weight	Adjusted body weight (any formula)
Loading dose for normal/underweight patients	○	○	○
Loading dose for overweight/obese patients	○	○	○
Maintenance dose for normal/underweight patients	○	○	○
Maintenance dose for overweight/obese patients	○	○	○

When dosing vancomycin, which dose cap (i.e., maximum dose) do you most commonly use in the following scenarios?

	2000 mg per dose	2500 mg per dose	3000 mg per dose	> 3000 mg per dose	No cap/maximum dose
Loading dose	○	○	○	○	○
Maintenance dose	○	○	○	○	○

APPENDIX 1 (con)

Confidential

How often do you use each of the following strategies when assessing vancomycin exposure and calculating further dosing?

	Rarely (< 10% of the time)	Sometimes (10-50% of the time)	Often (51-90% of the time)	Routinely (> 90% of the time)
Collect a post-loading dose level (within 6 hours) to ensure adequate vancomycin load	○	○	○	○
Use two-level kinetics following the first dose to calculate patient-specific pharmacokinetic parameters	○	○	○	○
Collect peak levels for pharmacokinetic calculations	○	○	○	○
Collect trough levels for pharmacokinetic calculations	○	○	○	○

When trough levels are collected in your PRIMARY PRACTICE ICU, how often are doses held pending level evaluation?

- ○ Doses are held routinely (> 90% of the time) pending level evaluation
- ○ Doses are held pending level evaluation only if kidney injury is suspected or known
- ○ Doses are held rarely (< 10% of the time), even if kidney injury is suspected or known
- ○ Trough levels are not used in my current practice

Which of the following best describes the target pharmacokinetic dosing and monitoring parameter used in your current practice for an ICU patient empirically prescribed vancomycin?

- ○ Trough
- ○ AUC
- ○ Trough and AUC

How often do you dose vancomycin via the following methods of administration?

	Rarely (< 10% of the time)	Sometimes (10-50% of the time)	Often (51-90% of the time)	Routinely (> 90% of the time)
Intermittent infusion	○	○	○	○
Continuous infusion	○	○	○	○

How comfortable are you assessing multiple vancomycin levels to calculate an area under the curve (AUC) for the following dosing strategies using two level kinetics after the first dose or at steady state?

	Not at all comfortable	Somewhat uncomfortable	Somewhat comfortable	Extremely comfortable
Intermittent infusion	○	○	○	○
Continuous infusion	○	○	○	○

APPENDIX 2. First-Order Equations for Vancomycin Pharmacokinetic Calculations

Patient-Specific Pharmacokinetic Parameters From First Dose

1. Step 1: Calculate patient-specific elimination rate (k).

$k = \frac{\ln(\frac{C_1}{C_2})}{T'}$ C1 = 1st random ~2 hours following completion of infusion

C2 = 2nd random ~12 hours following completion of infusion

T' = time between C1 and C2

2. Step 2: Calculate half-life (t1/2).

$t_{1/2} = \frac{\ln(2)}{k}$

3. Calculate Cmax:

$C_{max} = \frac{C_1}{e^{-k(\Delta T)}}$ C1 = 1st random ~2 hours following completion of infusion

ΔT = time between C1 and end of the infusion

4. Calculate volume of distribution (Vd)

$V_d = \frac{Loading\ Dose}{t} x \frac{1-e^{-kt}}{k\ x\ C_{max}}$ t= infusion time

5. Calculate Clearance (Cl)

$Cl = k\ x\ V_d$

6. Calculate total daily dose (TDD)

$TDD = Cl\ x\ AUC_{goal}$ AUC goal = 400-600 (use 500 in calculations)

APPENDIX 2 (con)

If not using first-dose kinetics:

1.) *k* is estimated by using the creatinine clearance (CrCl) [Cockcroft-Gault or Salazar-Corcoran if > 125% of ideal body weight] and the following equation: $k = 0.00083\ (CrCl) + 0.0044$

2.) V_d is estimated using 0.7 L/kg based on actual body weight

Calculating Intermittent Infusion

1. Calculate Dosing Interval (τ)

$$\tau = \frac{\ln(\frac{Cmax,desired}{Cmin,desired})}{k} + t$$

Cmax, desired: 40 mcg/mL

Cmin, desired: 10 mcg/mL

t = infusion time

2. Calculate the Maintenance Dose (MD)

$$MD = \frac{TDD}{\frac{24}{\tau}}$$

3. Calculate predicted Cmax based on MD and τ selected.

$$Predicted\ C_{max} = \frac{\frac{MD}{V_d}}{1 - e^{-k\,\tau}}$$

4. Calculate predicted Cmin based on Predicted Cmax.

$$Predicted\ C_{min} = Predicted\ C_{max}\ x\ e^{-k(\tau - t)}$$

t= infusion time

APPENDIX 2 (con)

Evaluating AUC of Intermittent Infusion at Steady State

Step 1. Calculate k

$k = \frac{ln\frac{C_{peak}^{ss}}{C_{trough}^{ss}}}{T\prime}$ T' = Determined by subtracting the time difference b/t C_{pk} and C_{tr} from τ

Step 2. Calculate half-life

$t_{1/2} = \frac{\ln(2)}{k}$

Step 3. Calculate C_{max} and C_{min} from C_{peak} and C_{trough}, respectively.

$C_{max} = \frac{C_{pk}}{e^{-kt\prime}}$ t'= time between C_{pk} as drawn and end of the infusion

$C_{min} = C_{tr}\ x\ e^{-kt\prime}$ t' = time between C_{tr} as drawn and true C_{min}

Step 4. Calculate Vd

$V_d = \frac{MD}{t} \text{x} \frac{(1-e^{-kt})}{k(C_{max})[1-e^{-k\tau}]}$ t= infusion time in hours

Step 5. Calculate Cl

$Cl = k\ x\ V_d$

Step 6. Calculate AUC

$AUC_{infusion} = \frac{(C_{max}+C_{min})}{2} x\ t$ t= infusion time

$AUC_{elimination} = \frac{C_{max} - C_{min}}{k}$

$AUC_{0-24} = (AUC_{infusion} + AUC_{elimination})\ x\ (\frac{24}{\tau})$

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Professional Positions
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Department of Pharmacy Practice and Science
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Clinical Pharmacist — July 2013-Present
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Honors

Society of Critical Care Medicine Presidential Citation	2019-2021
Kidney STARS Program, American Society of Nephrology	October 2020
Kentucky Society of Health-System Pharmacists Pharmacy Mentor of the Year Award	October 2020
Advances in Research Conference Trainee Grant, American Society of Nephrology	September 2020
Rho Chi Alumni Award, Alpha Xi Chapter	March 2020
Fellowship, American College of Critical Care Medicine	February 2020
Society of Critical Care Medicine Silver Metal Research Award	February 2020
Society of Critical Care Medicine Star Research Achievement Award	February 2018 & 2019
American College of Clinical Pharmacy Member Spotlight	January 2019
American College of Clinical Pharmacy Critical Care Practice and Research Network Publication of the Year	August 2018
CHEST Foundation Travel Grant	July 2018
Kentucky Society of Health-System Pharmacists New Practitioner of the Year	September 2014
Kentucky Society of Health-System Pharmacists Resident of the Year	October 2013
University of Kentucky Pharmacy Residency Impact Award	June 2013

University of Kentucky College of Pharmacy Outstanding Graduating Man Award	May 2011
University of Kentucky College of Pharmacy James Rhodes Award for Outstanding Commitment to Clinical Pharmacy Practice	May 2011
University of Kentucky College of Pharmacy Dean Earl P. Slone Award as Voted by the Student Body for Academic, Professional, and Social Accomplishments	May 2011 April 2010 April 2009
American Society of Health-System Pharmacists Student Leadership Award	March 2011

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Kressin C, Pandya K, Woodward BM, Donaldson C, **Flannery AH**. Ascorbic Acid in the Acute Care Setting. *JPEN J Parenter Enteral Nutr*. 2021 Mar 5 [online ahead of print]

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