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Accuracy of Therapeutic Drug Monitoring in Vancomycin and the Pharmacist Role: A Retrospective Case-series

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Thesis Summary

Through an observational, retrospective analysis of patient records, this thesis will analyze the accuracy of vancomycin dosing, discuss the burden vancomycin dosing places on pharmacists, and evaluate the utility of using vancomycin in the presence of newer therapies. This analysis compares initial trough level goals with true trough levels obtained from patients' lab values. This data will accompany a review of current literature and accounts of how vancomycin dosing affects pharmacy practice. Finally, therapies that can be used in place of vancomycin will be described.

Abstract

Vancomycin is a mainstay of therapy for treating virulent and resistant infections, especially methicillin-resistant *Staphylococcus aureus* (MRSA). However, vancomycin requires therapeutic drug monitoring (TDM) for optimal dosing and treatment. This requires pharmacists to calculate a dosing regimen that correlates to appropriate goal vancomycin concentrations in the blood. Dosing vancomycin can be difficult, as it varies on a patient's weight, renal function, age, etc. Doses may have to be adjusted in response to out-of-range concentrations, which requires further pharmacy calculations. Inaccurate dosing poses a risk to patient safety and places a resource and time burden on pharmacists. If vancomycin dosing methods do not prove to correlate with patient safety goals and therefore require further pharmacist intervention, then alternative antibiotic regimens could be considered. This article reviews the real-world accuracy of vancomycin dosing, the burden this dosing places on pharmacists, and the alternative antibiotics that may be used to replace vancomycin for certain indications.

Introduction

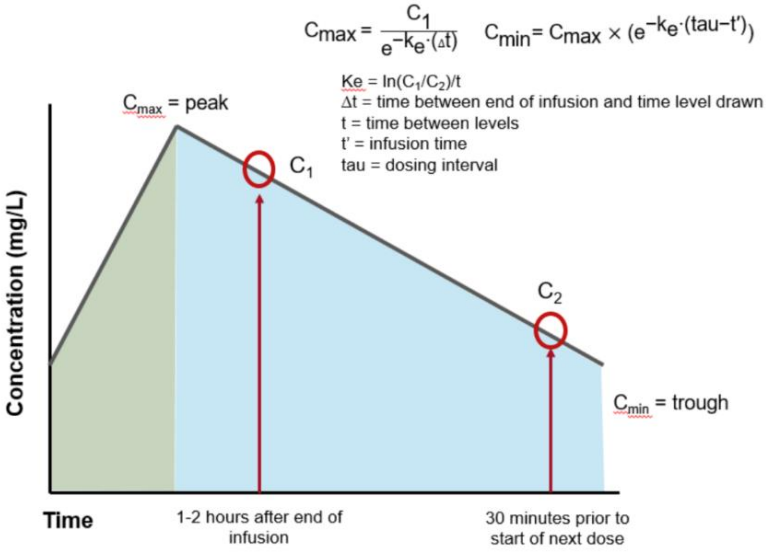
Vancomycin is frequently administered as empiric MRSA therapy in critically ill patients with MRSA risk factors. It works by inhibiting cell wall synthesis by binding to D-alanyl-D-alanine[1]. This antibiotic is the drug of choice for many infectious indications and has been included in clinical guidelines for treating bloodstream infections, meningitis, skin and soft tissue infections, and others. The rationale behind its prevalence is its excellent broad-spectrum, gram-positive organism coverage and wide distribution into body tissues. Vancomycin is also safe to use in liver dysfunction and does not require hepatic dose adjustments[1]. The downsides to vancomycin include the lack of gram-negative or anaerobic coverage and a narrow therapeutic index. Common adverse events caused by vancomycin include acute kidney injury (AKI), ototoxicity, and vancomycin infusion syndrome. Vancomycin is also intravenous use only (the oral formulation is only indicated for the treatment of *C. difficile* infections)[1]. Importantly, emerging resistance can limit its use. Vancomycin-resistant enterococci (VRE) is noted by the Center for Disease Control (CDC) to be a "serious threat" in the Antibiotic Resistance Threats in the United States 2019

report. VRE caused approximately 5,400 deaths in 2017, and it is estimated that 30% of all hospital-acquired enterococcal infections are vancomycin resistant[2]. There has also been a phenomenon described as an "MIC creep", where MICs for vancomycin in MRSA have been significantly increasing over time, indicating that the effectiveness of vancomycin against these strains is waning[3].

What makes vancomycin unique is the use of TDM to monitor drug clearance and activity. With a narrow therapeutic index, personalized therapy is critical. TDM is used to limit adverse events such as AKI while optimizing bactericidal activity. Vancomycin TDM utilizes equations incorporating patient body weight and height, age, and creatinine clearance to estimate the patient's exposure to vancomycin and their clearance of the drug. Trough and peak levels drawn after achieving steady-state can be used to further adjust dosing and create a better understanding of the patient's body kinetics. Steady-state for vancomycin typically occurs after the third dose[1]. Peak levels are therefore drawn an hour after the end of the third infusion, and trough levels are drawn an hour prior to (or right before the beginning of) the fourth infusion.

Multiple calculation methods exist, such as trough measurement only method, area under the curve/minimum inhibitory concentration ratio (AUC/MIC) method, and even Bayesian modeling, which is software that can more accurately estimate AUC/MIC values. AUC:MIC measures the area under the vancomycin clearance curve in relation to the minimum inhibitory concentration of vancomycin needed to be effective against a specific organism. AUC can best be described as the total exposure of a drug over a period of time. In 2020, the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists published consensus guidelines for therapeutic monitoring of vancomycin in serious MRSA infections. These guidelines recommended an individualized target of the AUC/MIC ratio of 400 to 600 (assuming an MIC of 1 mg/L)[4]. To calculate an AUC/MIC, a peak vancomycin level and a trough vancomycin level are obtained and plugged into pharmacokinetic equations (example of such is in Figure 1[5]). In order to effectively communicate goals to a medical team, pharmacists may estimate the trough value that corresponds to an AUC/MIC of 400-600 in a patient, and dosing will be adjusted to match this value.

Figure 1: Example of AUC/MIC calculations[5]



It is important to note that the 2020 guidelines are based on limited data, despite vancomycin dosing being studied for decades. None of the recommendations in these guidelines listed as high quality, or A-I[4]. This evidence limitation should instill caution in TDM utilization, and signals for the need for randomized controlled trials to further support these recommendations[6]. Previous 2009 guidelines recommended using trough-only monitoring (with a goal of 15-20 mg/L) as a surrogate for AUC/MIC targets. This was done for ease of managing therapy and simplifying dosing and monitoring. However, updated data has revealed that AUC/MIC estimations provided better patient safety and clinical efficacy. Despite this recommendation, the consensus guidelines do recognize that knowledge gaps still exist in determining the most optimal approach to vancomycin dosing[4].

TDM is not foolproof, and barriers to proper TDM execution exist. Not only do multiple TDM methods exist, but initial vancomycin dosing may also be based on physician preference and their clinical judgement. Additionally, critically ill patients have highly dynamic pharmacokinetics, which may result in imprecise TDM. Furthermore, if TDM is to be useful, it must be ordered on time, ordered for the precise draw time, collected properly, and interpreted correctly. This requires proper education of nursing, phlebotomy, pharmacy, laboratory technician, and physician staff. While TDM is a practical tool to ensure adequate drug concentrations are reached, it consumes time, money, and pharmacy staff resources to perform correctly. The utility of vancomycin should be assessed and compared to alternative antibiotics to evaluate if inpatient antimicrobial practices can be further optimized.

Methods

An observational, retrospective, single-center, case-series study was conducted using chart review via the EPIC electronic health record. Data from the Prisma Health Richland Hospital was collected from March 1st, 2021, to November 1st, 2021. Approval to collect patient data was approved by Prisma Health's Institutional Review Board on May 17th, 2022. Patients were included if they were 18 years of age or older, received IV vancomycin inpatient for at least 48 hours, and had at least one vancomycin level draw during the course of their therapy. Patients were excluded from analysis if they used oral vancomycin, were on dialysis treatment, initiated vancomycin prior to admission, were incarcerated, were transferred to another facility during treatment, or had missing data in their profile. Patients were also excluded if vancomycin levels were not drawn within 2 hours of the target draw time or if no pharmacy notes detailing vancomycin pharmacokinetics existed in their chart. The goal sample size was fifty patients.

The primary objective of this study was to analyze the accuracy of vancomycin calculations defined as the percent of initial trough levels in the goal range determined by pharmacist calculations. These initial trough value goals were determined by goal AUC/MIC

and patient pharmacokinetics. A secondary objective was to measure the burden of vancomycin dosing on pharmacists. This includes time burden, measured by the number of notes and frequency of required dosage changes. This study also evaluated if variables such as patient age, race, Charlson Comorbidity Score (CCS), body mass index (BMI), or treatment infection correlated to more frequent dosing changes. Finally, this study also examines if any increases in serum creatinine occurred during therapy.

Data points collected included patient demographics and comorbidities, baseline serum creatinine and peak serum creatinine during therapy, trough values, number of dosage changes, and number of pharmacy pharmacokinetics notes (see index for full data collection information). Most statistical analysis was descriptive in nature, due to the small sample size. A Pearson Correlation was used to analyze correlations for age, race, CCS, and BMI. A Wilcoxon Rank Sum test was used to analyze correlations for the variable of tretament indication. Statistics were calculated using the R Project for Statistical Computing.

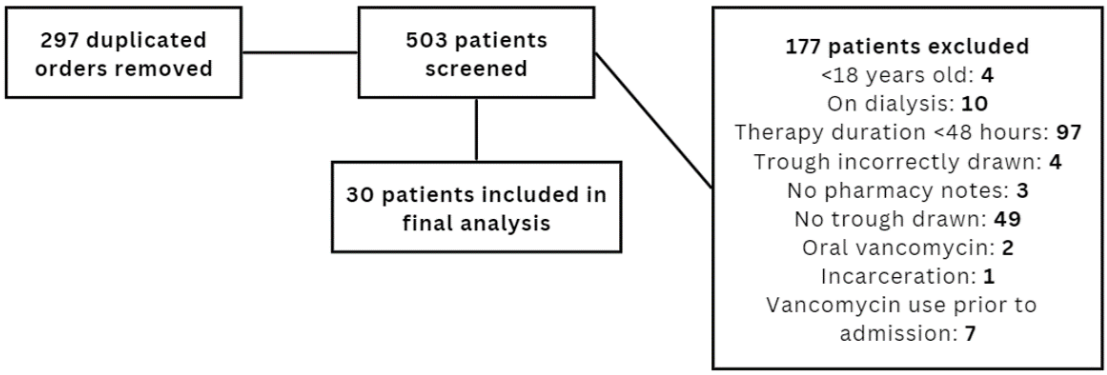
Results

A total of 503 patients were screened, and 30 patients were included in the final analysis due to time constraints (Figure 2). Males comprised 53% of the population and 50% of the patients were over the age of 60. The average age was 59 years of age, with a range of 30 to 91 years of age. Over half, 60%, of the patient population was African American. The mean Charlson Comorbidity Score was 3.5 and ranged from 0 to 8 (Figure 3). Only two patients had chronic kidney disease (CKD) at baseline and no patients had liver dysfunction. The average patient in this study was a 59-year-old African American male with multiple comorbidities (Table 1).

Table 1: Patient Demographics

Characteristic	*n = 30*	Percentage
Gender		
Male	16	53%
Female	14	47%
Age		
18-40	6	20%
41-59	9	30%
≥ 60	15	50%
Race		
Caucasian	12	40%
African American	18	60%
Other	0	0%
Liver Dysfunction	0	0%
Kidney Dysfunction	2	7%

Figure 2: Patient Screening Process



For the primary objective, only 12 patients had trough levels that were in goal, indicating that only 40% of initial doses accurately estimated patient kinetics. Additionally, 60% of patients had a change in dosing. Thankfully, most patients who had a dosage change required only one adjustment throughout their course of therapy in order to reach their goal levels. This indicates that while 60% of patients had to have their therapy adjusted, 43% (13 out of 30 patients) of regimens could be accurately reassessed. However, there were a number of patients who required greater than one dosage change during their course of therapy (Figure 4).

Figure 3: Charlson Comorbidity Score Distribution

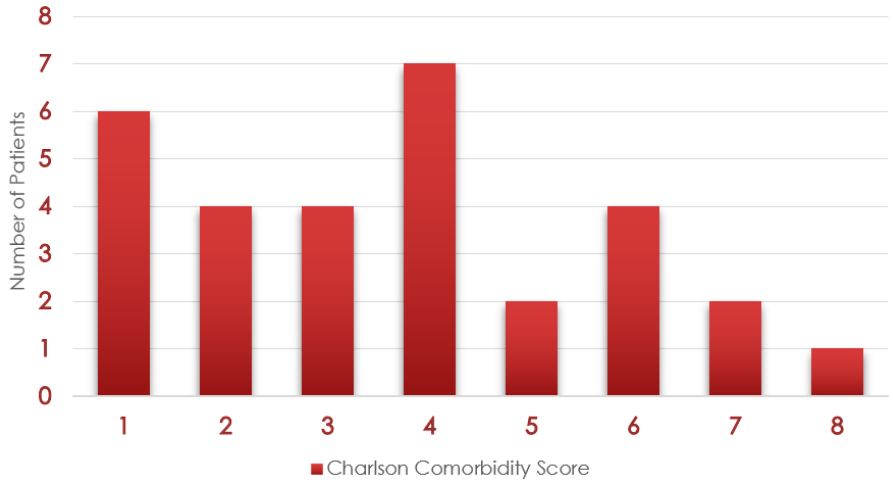
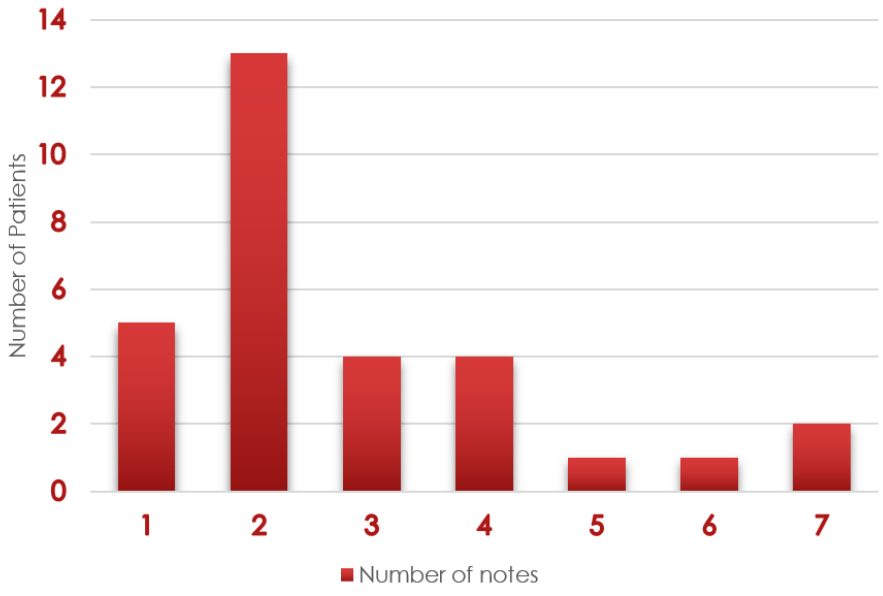


Figure 4: Indications and Dosage Changes

What was the treatment indication?	
Bacteremia	5 (17%)
CNS infection	1 (3.3%)
Endocarditis	2 (6.7%)
Osteomyelitis	2 (6.7%)
Pneumonia	7 (23%)
Skin and soft tissue infection	13 (43%)
Total dosage changes over course of therapy	
0	12 (40%)
1	13 (43%)
2	2 (6.7%)
3	2 (6.7%)
4	1 (3.3%)

Figure 5: Total Notes on Patient Profiles



For the secondary objective, the average number of notes left by pharmacists detailing vancomycin dosing pharmacokinetics and recommendations was 2.8 notes per patient. The majority of patients, 43%, had just 2 notes on their profile. However, other patients required extensive vancomycin monitoring, with some patients having up to 7 notes left on their profiles (Figure 5). Another secondary analysis was conducted to

evaluate if any patient characteristics correlated to more frequent dosing changes. Figure 6 illustrates how age relates to dosage changes, where R = 0.26 with a *p*-value of p = 0.16. In regard to race versus dosage changes, these variables do not correlate, as R = 0.12 and p = 0.52 (data not shown). Charlson Comorbidity Score (R= 0.098 and *p* = 0.61) and BMI (R = -0.093 and *p* = 0.63) did not have significant correlations to dosage changes (Figure 7 and Figure 8). Alternatively, a Wilcoxon-rank sum test showed that the coded indications are significantly correlated to total dosage changes. The indication of bacteremia has a higher mean (1.8 dosage changes) than any other indication (Figure 9). One patient with a skin and soft tissue infection had four dosage changes was an outlier.

Overall, patients generally did not have adverse kidney effects while on vancomycin. Only 17 patients experienced an increase in serum creatinine, with an average increase of only 0.16 mg/dL. A total of 2 patients had a serum creatinine increase greater than 0.3 mg/dL, which places them in Stage 1 AKI according to the AKIN criteria[6]. One patient experienced a serum creatinine increase of 0.68 mg/dL, and their initial trough was supratherapeutic at 35.9 mg/L.

Figure 6: Correlation Between Age and Frequency of Dosage Changes

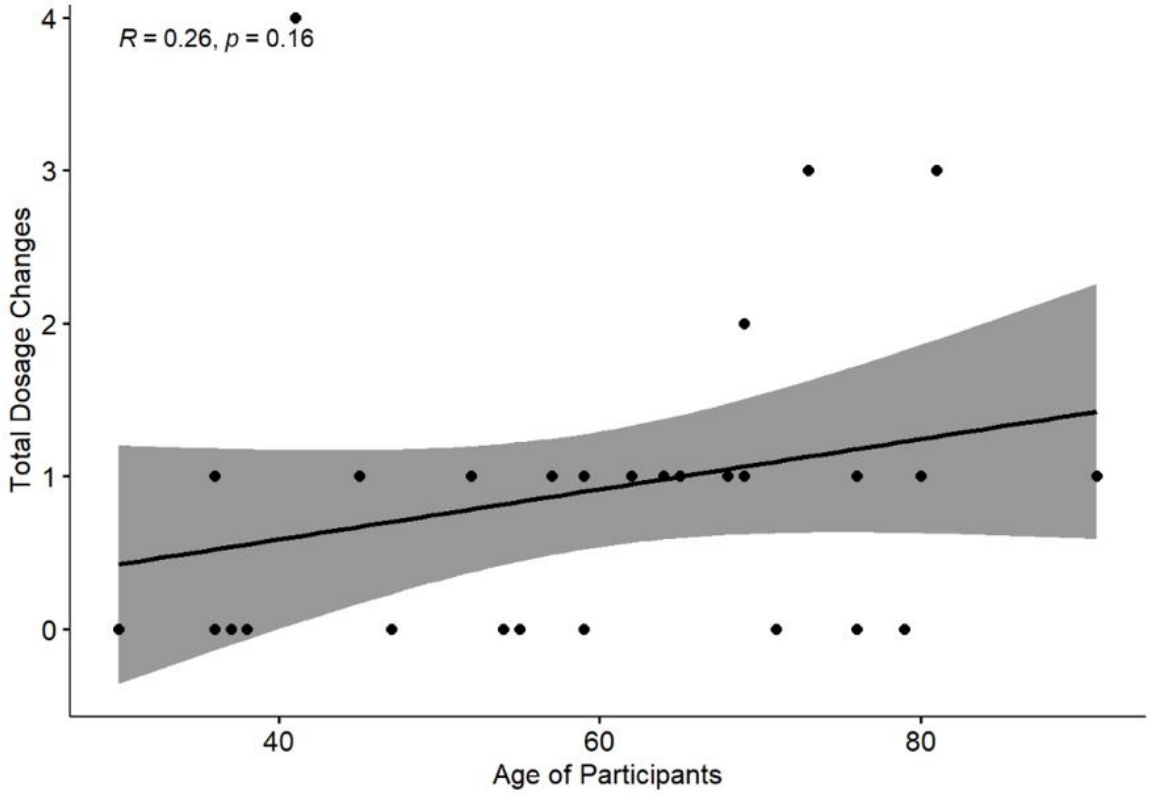


Figure 7: Correlation Between Charlson Comorbidity Score and Frequency of Dosage Changes

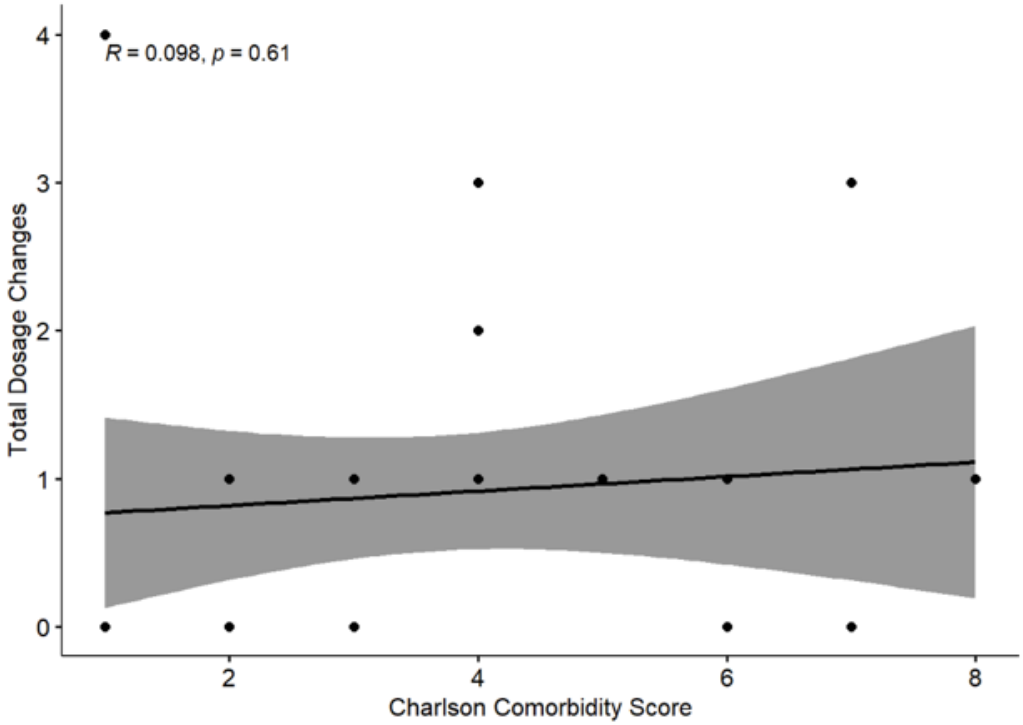


Figure 8: Correlation Between BMI and Frequency of Dosage Changes

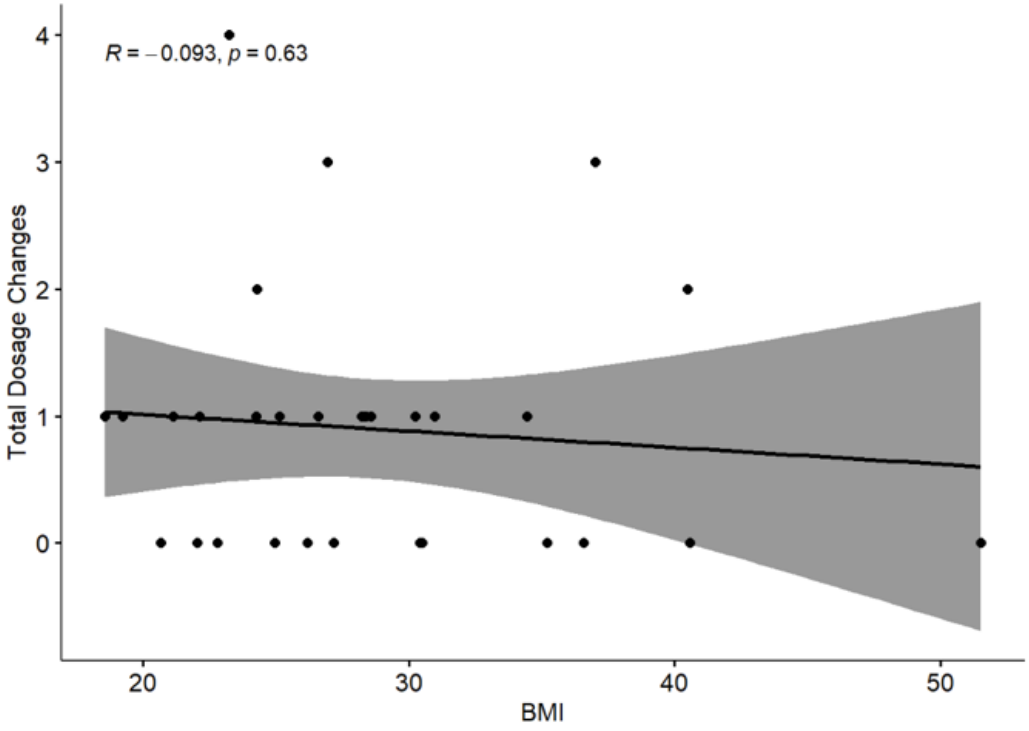
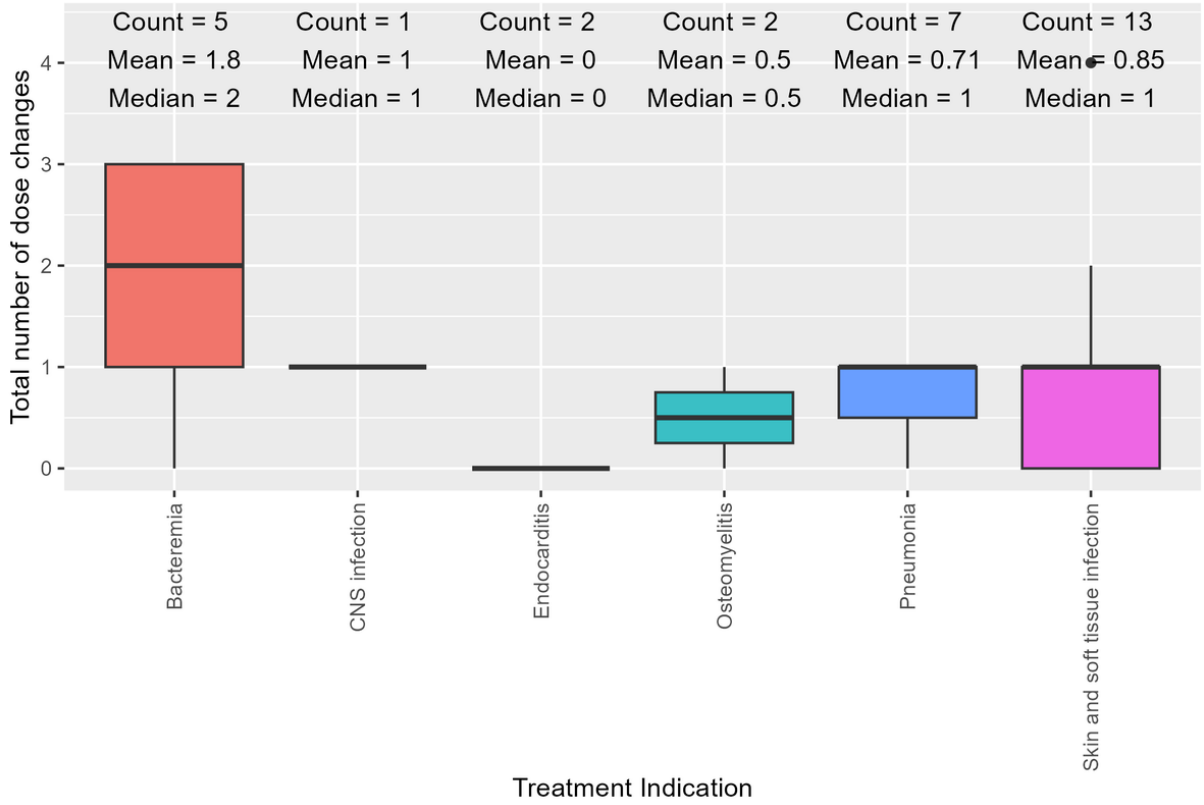


Figure 9: Indications versus Dosage Changes Box Plot



Discussion

This study has substantial external validity, shown by the diversity of studied patients. Gender and race were evenly represented, and a wide range of ages were included. A majority of patients were older than 60 years, however this may better represent the typical age for an admitted patient[7]. Other strengths of this study include the large proportion of patients with multiple comorbidities and the incorporation of any indication for intravenous vancomycin . A large proportion of patients were minorities, however minority groups other than African American were not able to be included. Inclusion of such a large proportion of minorities allows the analysis of genetic variations between races, even if this analysis was not big enough to make such conclusions. Unfortunately, no patients with liver dysfunction were added to the study population, which also limits the generalizability of the results. Furthermore, this study was small-scale, and the sample size limited the ability to draw statistical correlations. For example, one patient had increased serum creatinine while also having a supratherapeutic vancomycin trough. It cannot be determined if vancomycin caused kidney injury, or if a confounding factor caused the AKI, which reduced vancomycin clearance, and in turn resulted in an elevated trough. Moreover, while there may be a small numerical correlation in age, race, CCS, and BMI to dosage changes, the *p*-value is not significant. Finally, the

retrospective, observational, and single-center nature of the study limits the ability to identify correlations.

The overall results from this study suggest that vancomycin dosing strategies may not always accurately predict patient pharmacokinetics. Despite pharmacist intervention, only 40% of patients had initial troughs in the goal range, and more than half of patients required dosing adjustments. Furthermore, patients with bacteremia had a higher mean number of dosage changes, which suggests that patients with bacteremias may have more unstable pharmacokinetics and may need frequent adjustments. Time outside of the goal AUC/MIC range poses risks to the patient, such as ineffective therapy and opportunity for organisms to develop resistance, or conversely harm the patient and require changes in therapy to prevent further damage. Although, the majority of patients with dosage changes had quick reassessment by pharmacist and were adjusted appropriately. This shows that TDM for vancomycin is useful and effective, but not in every scenario.

It is important to recognize that the majority of vancomycin use is empiric[8]. Many patients are initiated on vancomycin in the emergency department, and therapy is narrowed or altered upon admission. In fact, the majority of patients, almost 55%, were excluded from the study for remaining on vancomycin therapy for less than 48 hours. Short courses of vancomycin do not allow for drug levels to reach steady state, and thus TDM is not accurate in these patients. With a majority of patients not requiring empiric therapy beyond 48-72 hours[8], many patients do not require TDM monitoring. There also exists a "paradox" in critically ill patients who receive vancomycin empirically. These patients frequently are admitted with physiologic derangements that may change in the span of a few days. Renal function may rapidly change from initial presentation, as well as volume of distribution. An estimated 20% of vancomycin volume of distribution is decreased after 72 hours, and the tissue penetration of vancomycin can vary widely in patients with sepsis[8]. Ensuring appropriate levels of vancomycin is essential in critical stages of illness, but the critically ill patient's shifting pharmacokinetics may render TDM of little value. In other words, reaching goal vancomycin levels is unlikely in the patient population where appropriate drug exposure is most important. It may be hard to justify using TDM guided strategies in all patients, particularly when TDM demands attention from pharmacists and clinicians.

To perform TDM, significant monetary and cognitive resources are required. For example, vancomycin pharmacokinetic notes are typically placed once daily. In this study, an average of 2.8 notes per patient indicated that pharmacists were actively monitoring therapy and updating their calculations over the span of several days. A number of patients required extensive vancomycin monitoring, with some patients having up to 7 notes left on their profile. A retrospective review found that pharmacists spent on average 40 minutes per patient dosing vancomycin. This time was divided into performing chart review on

each patient, interpretation of results, pharmacokinetic calculations, and also follow-up evaluation[9]. If this data is applied to this study, this adds up to an average of 112 minutes (almost two hours) per patient, with a range of 40 minutes to 280 minutes (over four hours) spent on dosing and monitoring vancomycin. Additionally, with the release of updated TDM guidelines comes the necessity to create new dosing and monitoring protocols. Much of this work is placed on pharmacists, and training of hospital staff is required after completion[8]. All of this added workload may distract pharmacists from performing other patient care activities.

In addition, collecting vancomycin troughs can be more challenging than expected. Proper collection time is vital, and this can be overlooked. For example, four patients in this study were excluded due to improperly drawn troughs. Another study performed at a large academic medical center measured 2,597 vancomycin levels to see what proportion of them were drawn inappropriately. The authors found that 41.3% of samples were drawn too early[10]. This may seem minute, but early levels can result in falsely elevated troughs, and can underestimate a patients drug clearance. These early draws caused providers to decrease, increase, discontinue, or hold a vancomycin dose, as well as order repeat levels[10]. These consequences can increase lengths of stay for a patient and increase their cost of care. Interrupting workflow in a clinical setting to perform extra TDM monitoring can also increase the risk of medical error[8]. Another study implemented nursing staff education regarding vancomycin and troughs. Prior to education, only 69% of troughs were collected appropriately. Post education, the proportion increased to 74%[11]. Proper education for nursing, phlebotomy, laboratory, and healthcare team staff may improve the utility of vancomycin TDM.

At times in clinical practice, patients will be switched from vancomycin to another therapy due to developing toxicity or their inability to reach goal trough levels. If this much effort by pharmacists is used dosing this drug, and goals are not always reached despite their efforts, it would not be a stretch to conclude that alternative therapies may be considered as empiric therapy in place of vancomycin, especially in patients who present with multiple disease states and unpredictable kinetics.

Next Steps: Considering Alternatives

Thankfully, due to drug development research, vancomycin is not the only broad-spectrum gram-positive antimicrobial. This review will focus on some of the more commonly used alternatives: linezolid, daptomycin, and ceftaroline. Notably, none of these agents require TDM monitoring. This list is not all inclusive, other antimicrobials such as tigecycline, dalbavancin, telavancin, oritavancin, quinupristin/dalfopristin exist. Refer to Table 5 for a summation of the following discussion.

Linezolid

Linezolid is a synthetic oxazolidinone that inhibits protein synthesis in bacteria by binding to the 50s ribosomal subunit. Remarkably, it has been hypothesized that antimicrobials that can inhibit protein synthesis have added efficacy against toxin-producing strains of bacteria[12]. The spectrum of this agent is very similar to that of vancomycin. Switching to linezolid would not shift coverage drastically: linezolid would add *S. saprophyticus* coverage, but lose *Actinomyces* spp. , *L. monocytogenes*, and *Nocardia* spp. coverage. The key difference in coverage is linezolid's activity against VRE, meaning it can be used in the setting of vancomycin failure[13]. Currently, linezolid is used to target *Staphylococcus* and *Streptococcus* spp., and has labeled indications for VRE treatment, community-acquired and hospital-related pneumonia, and skin and soft tissue infections (SSTIs). It has been used off-label for indications such as central nervous system (CNS infections), bacteremia, endocarditis, osteomyelitis, and others[1].

Table 2: Evidence for Linezolid (Selection)

Article	Design	Outcome Summary
Linezolid versus Vancomycin In Treatment Of Complicated Skin and Soft Tissue Infections[14]	-Randomized, open-label, comparator-controlled trial comparing clinical efficacies, safeties, and tolerability of linezolid and vancomycin - Linezolid (600 mg) Q12 IV OR PO, or vancomycin (1 g) Q12 IV	- Clinical cure: 92.2% with linezolid and 88.5% with vancomycin (P= 0.057) - ADEs reported similarly in both groups
Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia[15]	-Randomized, double-blind, controlled study assessing safety and efficacy of linezolid compared to vancomycin for MRSA nosocomial pneumonia - IV linezolid (600 mg every 12 hours) or vancomycin (15 mg/kg every 12 hours) for 7-14 days	-Clinical response significantly higher with linezolid, although 60-day mortality was similar -57.6% linezolid-treated pts were clinically cured at EOS, compared with 46.6% vancomycin-treated patients
Vancomycin versus Linezolid in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Meningitis[16]	-Single-center retrospective cohort study comparing microbiologic success with linezolid vs. vancomycin in MRSA confirmed meningitis	-Microbiologic success rates: linezolid 7/9 and vancomycin 2/8 (p=0.044) -Vancomycin was replaced with linezolid in six patients

Table 2: Evidence for Linezolid (Selection) Continued

Comparative Effectiveness of Vancomycin Versus Linezolid for the Treatment of Acute Pulmonary Exacerbations of Cystic Fibrosis[17]	-Retrospective cohort study analyzing effectiveness of linezolid vs. vancomycin in improving lung function during Cystic Fibrosis exacerbations	- No difference was observed in return to baseline FEV1 between vancomycin (80.3%) and linezolid (75.8%; P = 0.53) - No statistically significant prediction for improvement in lung function between groups (P > 0.05 for all)
EOS: End of stay; ADE: Adverse drug event; IV: Intravenous; PO: Oral; RR: Risk ratio; CI: Confidence interval; FEV1: Forced expiratory volume in 1 second		

Benefits of linezolid include lack of renal or hepatic dosing adjustments (unless creatinine clearance is ≥130 mL/minute/1.73 m2), and an oral formulation with high bioavalability[1]. The oral formulation creates an opportunity for patients to leave the hospital and finish their therapy outpatient, thereby decreasing hospital cost and risk of developing subsequent infections. Linezolid does have the ability to cause thrombocytopenia and serotonin syndrome. The mechanism behind serotonin syndrome involves linezolid's inhibition of monoamine oxidase. When used in combination with multiple serotonergic agents, it can induce toxicity[12]. Lactic acidosis, diarrhea, and peripheral and optic neuropathy have also been reported with linezolid use[1].

Daptomycin

Daptomycin is a cyclic lipopeptide that causes depolarization of cell wall membranes. Similarly to linezolid, the spectrum of activity is very comparable to vancomycin. By switching to daptomycin from vancomycin, only *Streptococcus anginous* and viridans group streptococci (VGS) coverage is lost. However, VRE coverage is gained[13]. Despite similarity in coverage, daptomycin cannot be used in any lung infections due to its inhibition by pulmonary surfactant. On the other hand, daptomycin does have labeled indications for SSTIs and bacteremia. The indication for bacteremia places higher value on daptomycin in context of this study. There is room for using daptomycin to possibly lessen the frequency of dosage changes compared to vancomycin. It is also used off-label for osteomyelitis, meningitis, endocarditis, and other infection sources[1].

While daptomycin does not require hepatic adjustments, renal dysfunction does alter daptomycin dosing. Furthermore, reports of interstitial nephritis with daptomycin therapy have been seen. The most common side effect of daptomycin is asymptomatic or symptomatic increases in creatine phosphokinase(CPK), which can indicate myopathy or rhabdomyolysis. Other adverse events such as eosinophilic pneumonitis, hypersensitivity, and peripheral neuropathy have been reported. Lastly, daptomycin is for intravenous use only[1].

Table 3: Evidence for Daptomycin (Selection)

Article	Design	Outcome Summary
The Efficacy of Daptomycin versus Vancomycin for Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection in Patients with Impaired Renal Function[18]	-Retrospective cohort study assessing treatment failure in MRSA bacteremia in daptomycin- vs vancomycin-treated subjects and the interaction with renal function.	-Daptomycin is not affected by GFR level and had similar efficacy to vancomycin -Using daptomycin in renal dysfunction was not associated with treatment failure (P= 0.54)
Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*[19]	-Open-label, randomized trial assessing clinical success rate of daptomycin vs. standard therapy for endocarditis - 6mg/kg daptomycin vs. low-dose gentamycin + antistaphylococcal PCN or vancomycin	-44.2% of daptomycin and 41.7% of standard therapy patients received successful outcomes (95% CI, −10.2 to 15.1%) -Daptomycin was noninferior to standard of therapy
Daptomycin versus Vancomycin for Complicated Skin and Skin Structure Infections: Clinical and Economic Outcomes[20]	-Prospective, open label study to assess effect of daptomycin vs. vancomycin In SSTIs -Prospective arm: daptomycin 4mg/kg Q24h -Historical controls: vancomycin dosed for troughs 5-10 mg/L	-Clinical improvement: 90% with daptomycin and 70% with vancomycin -Infection resolution: 98% with daptomycin and 81% with vancomycin -($P < 0.01$ for both)
Efficacy and Safety of Daptomycin versus Vancomycin for Bacteremia Caused by Methicillin-Resistant *Staphylococcus aureus* with Vancomycin Minimum Inhibitory Concentration > 1 µg/mL[21]	-Systemic review and meta-analysis comparing efficacy of daptomycin to vancomycin for MRSA bacteremia with elevated vancomycin MICs	-Daptomycin has significantly lower mortality (OR: 0.53, 95% CI: 0.29-0.98) and higher treatment success (OR: 2.20, 95% CI: 1.63−2.96)

GFR: Glomerular filtration rate; CI: Confidence interval; PCN: penicillin; OR: Odds ratio

Ceftaroline

Ceftaroline is a broad-spectrum fifth-generation cephalosporin that inhibits cell wall synthesis. Ceftaroline is the only cephalosporin to cover MRSA. This antimicrobial is different from the above antimicrobials due to a lack of *Enterococcus* spp. coverage, especially a lack of VRE coverage. Alternatively, ceftaroline's activity crosses over into gram-negative organism coverage, adding *E. coli, K. pneumoniae, H. influenza,* and *M. catarrhalis* to its target list[13]. While it is not a perfect dupe for vancomycin, it offers other benefits the previous two antimicrobials do not. Currently it is indicated for community-acquired pneumonia and SSTIs, and is not a first line agent[1]. However, some data suggests it may have other utilities, such as treating bacteremia.

Table 4: Evidence for Ceftaroline (Selection)

Article	Design	Outcome Summary
The Use of Ceftaroline Fosamil in Methicillin-Resistant *Staphylococcus aureus* Endocarditis and Deep-Seated MRSA Infections[22]	-Retrospective case-series of ten patients evaluating effectiveness of ceftaroline in MRSA endocarditis	-7/10 patients achieved microbiological cure and 6/10 patients achieved clinical cure -2/10 patients remained bacteremic and expired
Methicillin-Resistant *Staphylococcus aureus* Bacteremia and Endocarditis Treated with Ceftaroline Salvage Therapy[23]	-Retrospective case series of six patients on ceftaroline for MRSA bacteremia as salvage therapy following vancomycin of daptomycin failure	-All six patients had clearance of their bacteremia -No relapses were identified -No resistance was identified
CANVAS 2: The Second Phase III, Randomized, Double-Blind Study Evaluating Ceftaroline Fosamil for the Treatment of Patients with Complicated Skin and Skin Structure Infections[24]	-Randomized, double-blind study to determine non-inferiority of ceftaroline monotherapy to vancomycin + aztreonam in cSSSIs -600 mg of ceftaroline Q12 or 1g vancomycin + 1g aztreonam Q12	-MRSA cSSSIs were cured in 91.4% of patients in the ceftaroline group and 93.3% of patients in the vancomycin + aztreonam group -Microbiologic success occurred in 92.9% of ceftaroline patients and 95.0% in vancomycin + aztreonam patients
Anti-MRSA Cephalosporin versus Vancomycin-Based Treatment for Acute Bacterial Skin and Skin Structure Infection[25]	-Systemic review and meta-analysis comparing the safety and efficacy of ceftaroline to vancomycin-based regimens for SSTIs	-Clinical response rate was not significantly different (OR:1.05; 95% CI, 0.90–1.23) -For major cutaneous abscesses, ceftaroline had a lower response rate (OR: 0.62; 95% CI, 0.40–0.97)
cSSSIs: Complicated skin and skin structure infections		

Since ceftaroline is a cephalosporin, penicillin allergy must be considered. However, evidence shows that penicillin allergy cross-reactivity to cephalosporins is minimal. Some data says that this cross-reactivity occurs in 1-10% of patients with a penicillin allergy, with rare anaphylactic reactions only occurring <0.02% of the time[26]. Similarly to daptomycin, ceftaroline is for intravenous use only, requires renal function adjustments, but does not require hepatic adjustments. True to its drug class, the most common adverse events associated with ceftaroline are anemias and neurological reactions such as encephalopathy and seizures[1].

Table 5: Summation of Discussed Vancomycin Alternatives

Agent	Benefits	Considerations	Labeled Indications
Linezolid	• Oral dosing possible • No renal or hepatic dose adjustments • VRE coverage	• Thrombocytopenia • Serotonin Syndrome • Lactic acidosis • Neuropathy	• VRE • Pneumonia • SSTI • *Off-label: CNS infections, endocarditis, osteomyelitis, bacteremia, and others*
Daptomycin	• VRE coverage • No hepatic adjustments	• Requires renal dose adjustments • Not for pneumonia • Myopathy, neuropathy, pneumonitis, and nephritis	• Bacteremia • SSTI • *Off-label: osteomyelitis, meningitis, endocarditis, and others*
Ceftaroline	• Has more gram-negative coverage • No hepatic adjustments	• Requires renal dose adjustments • No VRE coverage • No *Enterococcus* spp. coverage • Anemias and neurotoxicity	• Pneumonia • SSTI • *Off-label: bacteremia*

Conclusion

This study analyzed the concordance of calculated vancomycin trough values based on AUC/MIC calculations to true trough values obtained from patients admitted to Prisma Health Richland Hospital for infections requiring intravenous antibiotics. The goal of this study was to evaluate the precision of TDM calculations with true trough levels, while concurrently assessing the burden that TDM places on pharmacy staff. In this population, vancomycin troughs were only accurate 40% of the time, and a majority of patients required dosage changes. Additionally, it was evident that pharmacists were spending a considerable amount of time on vancomycin dosing and monitoring. This analysis does not advocate for the eradication of vancomycin. Vancomycin has been used for decades and

retains clinical utility. However, the goal of this thesis was to raise awareness and encourage discussion around the challenges associated with implementing vancomycin TDM and alternatives to combat these concerns. Ideally, a prescribing physician can take their clinical expertise, combine it with the presented data, and decide if vancomycin is clinically appropriate for their patient. If alternative agents are indicated, consider the indication, infecting organism, susceptibilities from cultures, and patient tolerability and allergy before choosing an antimicrobial. Consult local antibiograms, local and national guidelines, pharmacists, and the antibiotic stewardship team. Some patients may benefit greatly from vancomycin, some may not be optimal candidates. For the latter, alternative antimicrobials would provide better long term outcomes, fewer adverse events from improper dosing, and result in less drug resistance. Furthermore, clinical resources could be better allocated to pharmacists to support other high-level patient care activities.

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Supplementary Information

1. **All data points collected in study period**
    a. Patient Demographics:
        i. Age
        ii. Race
        iii. Ethnicity
        iv. Gender
        v. Weight
        vi. Height
        vii. Comorbid conditions (Charlson Comorbidity Index)
    b. Patient serum creatinine at the start of vancomycin therapy
    c. Peak patient serum creatinine during vancomycin therapy
    d. Organism identified or indicated “None” if empirical use
    e. Vancomycin MIC (if known)
    f. Treatment indication (bacteremia, osteomyelitis, endocarditis, skin and soft tissue infection, CNS infection, pneumonia, or other)
    g. Time and date of first vancomycin dose
        i. Time and date of loading dose if administered
        ii. Time and date of maintenance dose
    h. Time and date of first drawn vancomycin serum concentration
        i. If peak and trough were drawn, time and date of both
    i. Time and date of last vancomycin dose

j. Initial vancomycin trough concentration that was measured
k. Estimated AUC based on initial vancomycin concentration(s)
l. Number of vancomycin concentrations that were obtained during treatment course
m. Was there a dosage or dosing frequency change prior to drawing the initial vancomycin concentration? (Yes/No)
n. Was there a dosage or dosing frequency change after drawing the initial vancomycin concentration? (Yes/No)
o. Number of dosage changes during the vancomycin treatment course
p. Number of notes left detailing vancomycin dosing pharmacokinetics and recommendations

2. Organisms identified (if any)

a. Coagulase-negative *Staphylococci*: 5
b. MRSA: 4
c. MSSA: 2
d. *Enterococcus spp.*: 2
e. *Streptococcus spp.*: 1
f. *Corynebacterium*: 1