

QATAR UNIVERSITY

COLLEGE OF PHARMACY

CLINICAL AND PHARMACOKINETIC EVALUATION OF OPTIMAL  
MONITORING PARAMETERS AND SAMPLING SCHEMES FOR  
VANCOMYCIN THERAPEUTIC DRUG MONITORING IN QATAR

BY

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## ABSTRACT

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Title: The Effect of Genetic and Non-Genetic Factors on Warfarin Dose Variability in Qatari

Population

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**Background:** Therapeutic drug monitoring (TDM) of vancomycin has been proven to maximize therapeutic outcomes and minimize toxicity when conducted appropriately. The quality of vancomycin TDM services in many settings remains to be explored. Vancomycin still poses many questions regarding its clinical pharmacokinetic parameters, optimal dosing, and TDM strategies in unstudied populations.

**Objectives:** This project comprised three distinct sequential phases. Phase I aimed to evaluate the appropriateness of routine vancomycin TDM service in Qatar and its impact on clinical outcomes. Phase II aimed to evaluate the relationship between vancomycin 24-hr-AUC/MIC ratios and cure; and to compare the clinical outcomes between peak-trough-based and trough-only-based vancomycin TDM approaches. Phase III aimed to determine vancomycin population pharmacokinetics considering patient-specific covariates and to assess the need for vancomycin dosing nomograms that are specific to Qatar's population.

**Methods:** Phase I was a retrospective chart review that was conducted on adult non-dialysis vancomycin TDM cases electronically documented between January 2014 and August 2016 in Al-Wakrah Hospital (AWH), Al-Khor Hospital (AKH), and Hamad General Hospital (HGH). Evidence-based criteria were applied to evaluate TDM appropriateness. Descriptive and

inferential statistical analyses were applied using SPSS v.23.

Phase II was a multicenter pragmatic parallel prospective randomized controlled trial (RCT) that was conducted from February 2016 to September 2016 in HGH, AWH and AKH. Adult non-dialysis patients who were initiated on vancomycin treatment were randomized to intervention arm (peak-trough-based vancomycin TDM) or control arm (trough-only-based vancomycin TDM). Multiple steady-state vancomycin blood samples were obtained for AUC determination. 24-hr-AUC calculation was conducted using NONMEM version 7.3 (ICON,USA) and PDx-Pop version 5.2 (ICON,USA), utilizing the population pharmacokinetic model developed in Phase III. Descriptive, inferential, and CART statistical analyses were applied using SPSS v.23.

Phase III was a population pharmacokinetic analysis that was conducted based on the principles of non-linear-mixed-effects-modeling. Internal validation of the final model was applied by bootstrap analysis of 500 data replicates. The agreement between the final parameter estimates, 95%confidence intervals of the developed final model and the bootstrap results were compared. To evaluate the need for population-specific dosing nomograms, the generated population parameter estimates were compared against literature reported values in similar populations. Phase III procedures were conducted using NONMEM v.7.3, (ICON,USA) and PDx-Pop v.5.2 (ICON,USA).

**Results:** Phase I: Two hundred eight vancomycin TDM cases involving 99 patients were evaluated. Most of the evaluated TDM cases (90.4%, n=188) were inappropriately conducted. The indications for TDM requests were appropriate in most of the cases (77.4%, n=161). Most of the blood samples were collected at incorrect times (70.7%, n=147), and incorrectly labelled

(81.7%, n=170). Overall, the actual sampling times revealed that most vancomycin blood samples (61.5%, n=128) corresponded to vancomycin random concentrations. Furthermore, high rates of inappropriate post-analytical actions were recorded (65.9%, n=137). Inappropriate compared to appropriate vancomycin TDM practices were associated with significantly lower therapeutic cures [47.3% vs .75%; p-value=0.009] and longer hospitalizations [median[IQR]: 26[31] vs. 13[47.7] days; p-value=0.103]. All patients who experienced neutropenia (100%, n=6) received inappropriate vancomycin TDM service. Similarly, of all patients who experienced nephrotoxicity, 84.6% (n=11) received inappropriate vancomycin TDM service.

Phase II: Sixty-five patients were enrolled in the RCT [trough-only-group:35 patients vs. peak-trough-group:30 patients]. Peak-trough-based vancomycin TDM was significantly associated with higher therapeutic cure rates compared to control group [76.7% vs .48.6%; p-value=0.02]. Compared to the control group, peak-trough-based vancomycin TDM recipients required less average vancomycin single doses and total daily doses by 370mg/dose and 927mg/day, respectively [p-value<0.05]. Similarly, trough-only-based vancomycin TDM recipients required higher cumulative vancomycin doses versus the intervention group [median[IQR]: 19500[25860] mg vs. 13250[14925] mg; p-value>0.05]. CART identified creatinine clearance(CrCl), 24-hr-AUC and TDM approach as significant determinants of therapeutic outcomes. All patients with  $CrCl \leq 7.85L/hr$  who achieved  $24-hr-AUC \leq 1255.98mg.hr/L$  and received peak-trough-based vancomycin TDM achieved clinical success [100%, n=19]. In contrast, patients with  $CrCl \leq 7.85L/hr$  who maintained  $24-hr-AUC \leq 1255.98mg.hr/L$  but received trough-only-based vancomycin TDM experienced 29.4% (n=5) failure rates.

Maintenance of 24-hr-AUC>564.117mg.hr/L was identified as the breakpoint of cure in trough-only-based TDM recipients [84.6%, n=11].

Phase III: A total of 769 vancomycin blood concentrations obtained from 156 subjects were analyzed. A two-compartment model with a proportional residual error and between-subject variability modeled on clearance (Cl), central compartment volume of distribution (Vc) and intercompartmental clearance (Q) best described vancomycin disposition. The physiologic parameters Cl and Vc, were estimated with good precision [Cl:5.23L/h, 95%CI: 4.72-5.74; Vc:44L, 95%CI: 37.7-50.3]. CrCl and age were significant covariates in the final model (p-value<0.01). Interindividual variability for Cl, Vc and Q was 38.9%, 42.7%, and 97% in the final model, respectively. Fixed effects parameters were estimated with reasonable precision and lied within 95%CI of bootstrap analysis. The population parameter estimates were similar to literature reported 2-compartment model estimates in adult non-dialysis patients.

**Conclusion:** This work suggests that the improvement of the quality of vancomycin TDM practices, maintenance of a 24-hr-AUC between 564.117-1255.98 mg.hr/L, and the implementation of peak-trough-based vancomycin TDM, are three main strategies that will potentially improve health-care outcomes associated with vancomycin treatment. The findings have important implications on developing strategies that will improve rational TDM practices in Qatar, the Middle East region and possibly worldwide

## DEDICATION

To my beloved family....

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I thank Allah, the Sacred and the Almighty, the most gracious, the most merciful, for His blessings and guidance throughout my life. Without His guidance and granting me the power and the ability, I would never have completed this work. I thank Allah with humbleness, gratitude and repentance that can never be expressed in words, and I ask Him to forgive my shortcomings and accept my deeds, one of them is this work.

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## ABBREVIATIONS

ABW: Actual body weight

ADR: Adverse drug reaction

AKH: Al-Khor Hospital

ALP: Alkaline phosphatase

ALT: Alanine transaminase

AOR: Adjusted odds ratio

ASHP: American Society of Hospital Pharmacists

ASP: Antibiotic stewardship program

AST: Aspartate transaminase

AST-C: Composite sampling time appropriateness

AST-LD: Appropriateness of sampling time relative to the last dose

AST-SS: Appropriateness of sampling time relative to attainment of steady-state

AUC: Area under concentration-time curve

AUC<sub>F</sub>: Area under concentration-time curve based on the full model

AUC<sub>PT</sub>: Area under concentration-time curve based on peak and trough concentrations

AUC<sub>T</sub>: Area under concentration-time curve based on trough concentration

AWH: Al-Wakrah Hospital

BMI: Body mass index

BSA: Body surface area

BSV: Between-subject variability

C<sub>1</sub>: First random serum concentration

C<sub>2</sub>: Second random serum concentration

CBC: Complete blood count

CA-MRSA: Community-acquired methicillin-resistant *S. aureus*

CART: Classification and regression tree

CA-VTDMS: Composite appropriateness of vancomycin therapeutic drug monitoring service

CHF: Swiss Franc

CI: Confidence interval

CL: Clearance

$C_{\max-ss}$ : Maximum serum concentration at steady-state

$C_{\min-ss}$ : Minimum serum concentration at steady-state

CNS: Central nervous system

$C_{\text{peak}}$ : Peak concentration

CrCl: Creatinine clearance

$C_{\text{trough}}$ : Trough concentration

CV: Coefficient of variation

EBE: Empiric Bayes estimates

EMR: Electronic medical record

FOCE-I: First order conditional estimation with interaction

GISA: Glycopeptide intermediate resistant *S. aureus*

HAP: Hospital-acquired pneumonia

Hgb: Hemoglobin

HGH: Hamad General Hospital

HMC: Hamad Medical Corporation

Hr: hour

HVISA: Heterogenous vancomycin resistant *S. aureus*

IBW: Ideal body weight

ICU: Intensive care unit

IDSA: Infectious Disease Society of America

IE: Infective endocarditis

IRB: Institutional Review Board

IQR: Interquartile range

IV: Intravenous

Kg: Kilogram

L: Litre

LBW: Lean body weight

LOCB: Last observation carried backward

LOCF: Last observation carried forward

LOS: Length of hospitalization

LRTI: Lower respiratory tract infection

MDRO: Multiple drug-resistant organism

MICU: Medical intensive care unit

MENA: Middle east and north Africa

Mg: Milligram

MRSA: Methicillin resistant *S. aureus*

MRC: Medical Research Center

NSAID: Non-steroidal anti-inflammatory drugs

NLMEM: Nonlinear mixed effects modeling

OFV: Objective function value

PD: Pharmacodynamic

PETINA: Particle-enhanced turbidimetric inhibition immunoassay

PK: Pharmacokinetic

PPK: Population pharmacokinetics

PREDPP: Prediction of population pharmacokinetics

Q: Intercompartmental clearance

QU: Qatar University

RCT: Randomized controlled trial

RSE: Relative standard error

RUV: Residual unexplained variability

$\sigma$ : Residual unexplained variability

SCr: Serum creatinine

SD: Standard deviation

SE: Standard error

SICU: Surgical Intensive Care Unit

SIRS: Systemic inflammatory response syndrome

SPSS: Statistical Package for Social Science

SS: Steady-state

SSTI: Skin and soft tissue infections

$T_{1/2}$ : half life

TBW: Total body weight

TICU: Trauma intensive care unit

USA: United States of America

USD: United States dollars

VBS: Vancomycin blood specimen/sample

$V_d$ : Volume of distribution

$V_c$ : Volume of distribution in central compartment



VISA: Vancomycin intermediate resistant *S. aureus*

VL: Vancomycin level

V<sub>p</sub>: Volume of distribution in peripheral compartment

VPC: Vancomycin peak concentration

VPL: Vancomycin peak level

VRC: Vancomycin random concentration

VRL: Vancomycin random level

VTC: Vancomycin trough concentration

VTL: Vancomycin trough level

$\omega$ : Intraindividual variability

WBC: White blood cell count

## CHAPTER 1: INTRODUCTION

### 1.1 Epidemiology of Methicillin resistant *S.aureus* (MRSA) infections

Multi-drug resistant organisms (MDRO) are a major cause of fastidious infections worldwide. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been reported to be the most common cause of MDRO infections (1), making it a significant universal etiology of complicated bacterial infections. According to the 8<sup>th</sup> International Congress of German Society of Hospital Hygiene, the prevalence of MRSA in the European continent is on the rise (2). Within the European Union (EU), surveillance data reported that more than 50% of *Staphylococcus aureus* (*S. aureus*) isolates were MRSA. Such infections were reported to affect at least 150,000 individuals yearly (3). In Canada, a population surveillance reported MRSA as a causative pathogen in 1 per 5 cases of *S. aureus* bloodstream infections between 2005 and 2006 (4). More importantly, a significant increase in the annual MRSA bacteremia cases was reported between 2000 and 2006 (4). A prospective study amongst infective endocarditis (IE) patients from 2000 to 2006 showed that MRSA was the causative pathogen in 22% of confirmed IE cases (5). Similarly, Mera and colleagues studied the trend of *S. aureus* infections in the USA, utilizing data from the Surveillance Network database (Eurofins Medinet) and the National Hospitalization Discharge Survey for the period 1998 to 2007 (6). Of 1,761,991 *S. aureus* isolates from the 10-year study period, the rate of MRSA in the USA increased from 32.7% in 1998 to 53.8% in 2007 (6). These findings are confirmed by the report of Mcgeer and colleagues, indicating that the number of MRSA cases increased by 16-fold during the past years (7).

The epidemiology of MRSA in Asian, African and Middle Eastern populations is showing similar trends of increase with time in recent years. In Taiwan, the resistance rate among 501 *S. aureus* isolates across 2 years (January 2010 -December 2011) was 50.3% (8). It was reported that MRSA was isolated from 14% of 215 adult patients with confirmed community-acquired *S. aureus* bacteremia (9). The prevalence of MRSA gradually increased between the years 2006 and 2008, and was the most common pathogen in necrotizing fasciitis (NF) during 2008, contributing to 19.8% of all *S. aureus* cases (10). Yoon et al. reported the prevalence of MRSA in a tertiary care hospital in Korea to be 31.3% cases of *S. aureus* IE between 1986 and 2004 (11). In Japan, the epidemiology of MRSA showed a trend of increase, as per the report of the 8<sup>th</sup> International Congress of German Society of Hospital Hygiene (2). Li and colleagues reported the epidemiology of complicated skin and soft tissue infections (SSTI) in hospitalized patients in China during 2008 to 2013; staphylococcal species were the most common isolates of all gram-positive complicated SSTIs, of which approximately 20% were reported to be resistant to methicillin (MRSA) (12). Similarly, high rates of MRSA infections were reported in the Middle East and Africa (MEAA) (13). During 2013, Zigmond's group conducted a systematic review and meta-analysis in which they included all studies reporting MRSA infection rates in MEAA; 23,170 MRSA isolates from 15,789 subjects across 84 published studies were explored (13). MRSA infections accounted for 48.8% of all reported *S. aureus* infections, which manifested as bacteremia (46.9%), SSTI (42.1%), as well as bone and joint tissue infections (57.33%) (13). Notably, the highest incidence of MRSA

infections was documented in the Arabian Peninsula (66.4%), followed by the Middle East and North Africa (MENA) region (~47-48%), which reflected into statistically significant differences when compared to other regions within the MEAA [24.4-40.4%] (13). Notably, the crude mortality of MRSA cases in 4,444 subjects was estimated to be 43.8% [95% confidence interval (CI): 36.1%-51.6%] in the MEAA (13). Collectively, these findings reaffirm that MRSA is a universal public health challenge.

Overall, the available statistics highlight the worldwide burden of MRSA infections on nations, and project a continuing increasing trend and threat to healthcare systems, warranting evidence-based effective preventative and therapeutic strategies.

## 1.2 The clinical and economic burden of MRSA infections

### *1.2.1 Morbidity and mortality of MRSA infections*

Compared to other gram-positive infections, MRSA infections are associated with more severe clinical presentations and complications. MRSA causes bloodstream invasive infections, skin and soft tissue infections (SSTIs), infective endocarditis (IE), pneumonia, and meningitis. The clinical complications of suboptimally treated MRSA infections such as embolism, heart failure, amputation, septic/cardiovascular shock, infection metastasis, requirement of mechanical ventilation, and the emergence of multiple antibiotic resistance, depend on the site infected (5, 10, 11, 14). This highlights the importance of timely initiating adequate antibiotic therapy that achieves bactericidal activity and complete cure, resulting in significant cost-

savings and less days of hospitalization. Thus, strategies that achieve timely effective antimicrobial management are warranted to improve the clinical and economic outcomes of MRSA infections.

In recent years, the morbidity of MRSA was further amplified by the increased rates of recurrent and persistent MRSA infections that are considered as therapeutic failures, despite antibiotic therapy. Compelling evidence suggests that persistence or recurrence of MRSA infections can be attributed to suboptimal antimicrobial treatment, which contributes to the emergence of glycopeptide-intermediate *S. aureus* (GISA) including vancomycin intermediate resistant *S. aureus* (VISA) strains (14-16). Persistent bacteremia, defined as positive microbiological cultures or persistent symptoms post 48 hours of adequate antimicrobial therapy, was reported to be significantly higher in patients with MRSA compared to methicillin-sensitive *S.aureus* (MSSA) (5). This finding was confirmed by Yoon and colleagues, who reported that patients with MRSA were 10 times more likely to have persistent bacteremia compared to MSSA (11). The rate of persistent or recurrent MRSA bacteremia was 12.9% amongst all MRSA bacteremia cases documented from 1995 to 2003, which was associated with significantly higher prevalence of GISA isolates (16). In another study comparing MSSA versus MRSA IE cases, higher MRSA bacteremia persistence rates were reported, reaching up to 26% (5). MRSA bacteremia is in many cases a complication; a consequence of inappropriately or inadequately treated focal MRSA infection, which explains the higher risk of bacteremia in MRSA infections. These statistics question the effectiveness and appropriateness of current MRSA therapeutic practices, necessitating

further exploration.

Furthermore, current evidence reports high mortality rates associated with MRSA infections. MRSA-attributable deaths were estimated to equate to a decade of years of life lost (17). A meta-analysis of 31 cohort studies with a pooled enrollment of 3,693 subjects found that all-cause mortality rates were significantly higher in MRSA bacteremia group (n=1360; 34.3%), with an odds ratio (OR) of 1.93 [95% CI: 1.54–2.42] compared to MSSA bacteremia (18). More importantly, the pooled analysis exploring death attributable to bacteremia showed that MRSA was associated with about two times mortality risk [OR=2.2; 95% CI: 1.2–3.8] (18).

### *1.2.2 The socioeconomic burden of MRSA infections*

The high morbidity and mortality associated with MRSA infections imposes significant societal and economic burden to healthcare systems globally. Compared to other gram-positive infections, MRSA presents higher socioeconomic burden on healthcare systems. For instance, patients with MRSA infections versus those with MSSA infections have significantly longer hospitalizations (19), which translates into considerable negative economic burden on healthcare systems and the society. The economic burden imposed by MRSA infections on healthcare institutions is related to the prolonged length of hospitalizations, increased healthcare resources utilization, more expensive treatments, isolation requirements as well as loss of productivity due to death and absenteeism from work (20-23). Additional yearly healthcare associated costs of €380 million within the European continent hospitals are attributed to MRSA infections (3). Eleven studies

from Europe, USA, and Canada showed that the sum of direct and indirect medical costs per MRSA case ranged between €2730 and €26514 (24). In a study aiming to estimate the yearly cost burden of MRSA in German hospitals, Claus et al. reported that the direct medical costs associated with MRSA infections ranged between €354.29 million and €1.55 billion (21). This huge economic burden is associated with loss of productivity due to long duration of illness, which is quantified at minimum to equate to €92.77 million (21). Another study showed that MRSA bloodstream infections contributed to substantially longer hospitalizations, estimated to exceed 400 extra months for multi-resistant bacteremia, collectively (25). Moreover, the mean duration of hospitalization was approximately 40 days for MRSA bacteremia compared to approximately 9 days for general MRSA positive cases [p-value<0.0001], corresponding to additional costs of €6372 (22). In a 700-bed tertiary Dutch hospital admitting 22,400 persons annually, the mean number of isolation days per MRSA cases was 4.5 days, summing to 333 days yearly and accounting for an annual extra cost of €2313 (22). Similarly, MRSA imposes a significant burden on the healthcare system in Switzerland, where the extra length of hospitalization days due to MRSA was 11.5 days [95% CI: 7.9-15]; mean daily costs per bed were 1.49 folds higher for MRSA infected cases compared to general acute ward cases, accounting for excess cost of 800 Swiss Francs daily (26). Furthermore, additional inpatient costs due to antibiotic resistant bacterial infections exceeded €900 million in 2007 in European Union, Iceland as well as Norway; loss of productivity due to death and loss of working days was estimated to equate at least €600 million each year across the European Union (23). These findings are consistent

with the 2007 joint report of the European Centre for Disease Prevention and Control and the European Medicines Agency that jointly documented that MRSA cases resulted in 10,50,000 additional hospitalization days yearly in the European continent (23).

The socioeconomic burden of MRSA has shown similar trends in the North America. In Canadian hospitals, the average number of extra hospitalization days per MRSA case was estimated to be 14 days, with the cost of MRSA management estimated to range from 42 million to 59 million USD yearly (20). A recent study in Canada involving various geographical regions reported that acute MRSA SSTIs were major contributors to the cost burden of diseases, with length of stay (LOS) ranging from 7.7-13.4 days in patients hospitalized with the primary diagnosis of MRSA-SSTI compared to 18.2-25.2 days in patients diagnosed with MRSA secondary to another main diagnosis resulting in initial hospitalization (27). In USA, the rate of MRSA related hospitalizations increased by two-fold in 2007 compared to 1998 (6). Elsewhere, the median hospital cost per MRSA episode was reported to be more than USD 25,000, excluding the costs of readmissions for patients with osteomyelitis and bacteremia (28). As per the economic simulation model by Lee et al., the median range of total mortality cost and loss of productivity cost per community-acquired MRSA case were USD 4666 - 17387 and USD 4704 - 17418, respectively (29). Furthermore, it was estimated that the annual burden of MRSA from societal perspective including indirect costs of loss of working hours/day was USD 8.7 million (30).



### 1.3 Vancomycin in the treatment of MRSA infections

Vancomycin is a glycopeptide bactericidal antibiotic that is widely used to treat serious gram-positive bacterial infections, particularly MRSA (31, 32). Vancomycin is a tricyclic bactericidal glycopeptide antibiotic that inhibits the synthesis of bacterial cell wall and impedes the RNA synthesis (33). Vancomycin is active against gram-positive bacterial strains and is used clinically to treat infections caused by penicillin resistant strains or in penicillin-sensitive strains in penicillin allergic patients (33). The main adverse effects of vancomycin are neutropenia, nephrotoxicity, ototoxicity and infusion-related red man syndrome (33).

MRSA presents a therapeutic challenge since it is resistant to a wide range of antibiotic options, including beta-lactams, quinolones, and macrolides (15), leaving vancomycin as the gold standard treatment of endovascular infections with empirical or confirmed MRSA (34). The global increased rates of MRSA have resulted in increased use of vancomycin, making it one of the most indispensable antibiotics in the setting of infectious disease (11, 35-38). Despite its proven effectiveness when target plasma exposure is achieved (39), recent studies have reported suboptimal clinical outcomes associated with vancomycin use, including prolonged hospitalizations, clinical failures, infection persistence/reoccurrence, and mortality (9, 11, 34, 40-42). Inappropriate use of vancomycin is a potential contributor to therapeutic failures that has not been investigated in most of these studies, but has been well-documented in quality audits (43-45).

The status of MRSA infections management with vancomycin in Asia and the MENA region is of special concern, since it was found that the trend

of VISA epidemiology has increased since 1997, with higher incidence rates of VISA strains documented in Asia compared to other continents (14). MRSA strains with reduced susceptibility to vancomycin present a global clinical and socioeconomic threat due to their higher association with therapeutic failures, prolonged hospital stay and recurrent bacteremia (14). Bacterial resistance to vancomycin is a probable consequence of inappropriate use of vancomycin as well as the application of vancomycin dosing and monitoring practices that are not generalizable to the respective (e.g. Asian/MENA) population/setting (14). These findings call into question the appropriateness of vancomycin therapeutic drug monitoring (TDM) practices in unexplored clinical settings. Also, it raises questions regarding the best TDM approaches for achieving optimal vancomycin plasma exposure that results in cure and prevents the emergence of resistant strains in the MENA region.

#### 1.4 Therapeutic drug monitoring of vancomycin

TDM deals with designing individualized drug dosage regimens based on patient-specific pharmacokinetic parameters to maximize therapeutic outcomes and minimize toxicity (31, 46, 47). TDM of vancomycin is essential in ensuring the attainment of positive clinical outcomes (efficacy) and minimizing nephrotoxicity (31). Vancomycin clinical pharmacokinetic parameters exhibit large inter-individual variability even with identical dosing regimens (48). Traditionally, the peak-trough approach, in which the steady-state peak and trough concentrations are measured, was used in vancomycin TDM. In 2009, a paradigm shift in clinical vancomycin dosing and monitoring practices occurred, following the

release of a consensus guideline jointly by the American Society of Health-System Pharmacists (ASHP), the Society of Infectious Diseases Pharmacists, and the Infectious Disease Society of America (IDSA). Based on limited clinical data and animal studies, vancomycin was considered “concentration-independent” and thus peak concentration monitoring was not recommended. Additionally, a 24-hour area-under-concentration-versus-time-curve (AUC) to minimum inhibitory concentration (MIC) ratio ( $AUC_{0-24}/MIC$ ) of  $\geq 400$  was defined as the target surrogate to attain clinical effectiveness. The 2009 guidelines recommended that steady-state (SS) trough concentrations be monitored as a surrogate for achieving  $AUC_{0-24}/MIC$  of  $\geq 400$ . Years following 2009, published evidence called into question the 2009 guidelines target ratio ( $AUC_{0-24}/MIC \geq 400$ ), as different AUC/MIC ratios have been found to achieve clinical effectiveness ([28](#), [34](#), [49](#)). This reported variability in AUC/MIC breakpoints may be attributed to the genetic variability between MRSA strains across different geographical areas ([8](#), [41](#), [50-52](#)), the variability in MRSA site of infection, and the variability of the populations studied in-terms of comorbidities and ethnicities ([53](#)). Hence, the generalizability of the published literature remains limited to different disease states, geographical regions and populations. Also, recent studies questioned the use of vancomycin trough level as an indicator of  $AUC_{0-24}/MIC$  optimal exposure, as discrepancies between optimal  $AUC_{0-24}/MIC$  ratios and the associated trough concentrations have been reported ([48](#), [54](#), [55](#)). Collectively, these studies raised concerns regarding the optimal vancomycin  $AUC_{0-24}/MIC$  breakpoint for cure, and the best vancomycin TDM approach that would result in the timely attainment of the optimal

AUC/MIC ratio associated with clinical effectiveness. To the best of our knowledge, no head-to-head randomized controlled trials (RCTs) have been previously conducted to compare between the traditional peak-trough-based vancomycin TDM approach and the 2009 IDSA-ASHP consensus guidelines (i.e. trough-based vancomycin TDM approach).

### 1.5 Significance and limitations of current TDM practices

Evidence has shown that efficient TDM practices result in decreased morbidity, mortality, LOS, treatment duration, need for extra treatments, as well as drug-related adverse events (56-62). These positive outcomes have resulted in considerable cost-savings from a healthcare system perspective (61, 62), resulting in the widely expanding application of TDM services throughout the world (63-70). However, the application of TDM services remains suboptimal in many clinical settings, hindering the attainment of the successful outcomes (71-75). In particular, studies have reported high rates of inappropriate TDM practices worldwide, in terms of indications for the TDM, blood sampling time, and subsequent dosing adjustment recommendations. This highlights a potential waste of resources (e.g. assays used and personnel time) and may partly explain the negative clinical outcomes observed with vancomycin treatment.

In Qatar, the healthcare model and clinical practice have considerably advanced in the past years. Part of this advancement in healthcare services is the provision of TDM service. TDM service in Qatar is largely influenced and undertaken by different healthcare professionals and personnel. However, hospital pharmacists have reported high rates of self-perceived incompetency in clinical pharmacokinetic knowledge and skills with their

minimal participation in TDM in clinical settings in Qatar (76). Therefore, potential opportunities of optimization of vancomycin TDM services in Qatar exist, as studies have shown that pharmacist-provided TDM services significantly improved clinical outcomes and TDM appropriateness (57, 58, 70).

### 1.6 Rationale of the study

Current literature presents conflicting evidence regarding the relationship between vancomycin serum concentrations, pharmacokinetic indices, and clinical efficacy outcomes. Consequently, approaches to monitoring vancomycin serum concentrations and providing dosing adjustments vary between different clinical settings; and questions still remain regarding the optimal AUC/MIC ratio associated with desired clinical outcomes as well as the best vancomycin sampling schemes to predict  $AUC_{0-24}/MIC$ . Limitations of the published literature related to these issues include small sample size, variations in MIC testing techniques, and the non-experimental nature of most study designs. Although the 2009 consensus guidelines recommend trough-only monitoring of vancomycin (32), to the best of our knowledge, no prospective RCTs have been conducted to compare the clinical and pharmacokinetic outcomes between the traditional peak-trough-based vancomycin TDM approach and the 2009 IDSA-ASHP guideline recommended trough-only-based vancomycin TDM approach. Also, an important gap in the literature is the lack of studies that determine vancomycin pharmacokinetic parameters in our Qatar population. Such studies are needed since no evidence has proven the external validity (i.e. the generalizability) of published vancomycin dosing guidelines and nomograms

to our population. Therefore, we aim to fill these gaps in the literature through the present study.

The population in Qatar is diverse and multiethnic. Although no study has been conducted to evaluate vancomycin dosing and TDM practices in Qatar, many clinicians report employing the IDSA 2009 vancomycin dosing and monitoring recommendations ([32](#)). Other clinicians follow the traditional peak-trough vancomycin monitoring approach. The clinical outcomes of both approaches in our population and clinical settings are unknown. Yet, anecdotal evidence has shown huge variations in serum levels with considerable numbers of sub-therapeutic and supra-therapeutic vancomycin levels witnessed by clinicians in the local setting. This would potentially contribute to therapeutic failures, increase in resistance patterns, nephrotoxicity, and increased economic burden on the healthcare system in Qatar. Whether these discrepancies are due to non-adherence to evidence-based dosing recommendations or due to local and inter-patient variability remains unknown. All published data are from other regions of the world, which quizzes the external validity of the findings to the local setting. This project will be the first to fulfill the needs for local and population-specific vancomycin studies in Qatar. Such studies are crucial to guide evidence-based setting and population-specific vancomycin dosing and monitoring practices. This will potentially reflect in maximizing efficacy, minimizing toxicity, and decreasing costs associated with vancomycin treatment in MENA region and elsewhere.

## 1.7 Study goal and objectives

This project comprises three distinctive study phases, with each having its specific objectives. First, a multicenter retrospective chart review was conducted to assess the appropriateness of routine vancomycin TDM service in Qatar and to determine the impact of the current vancomycin TDM practices on clinical outcomes. Second, a prospective RCT was conducted to compare the clinical and pharmacokinetic outcomes of peak-trough-based versus trough-only-based vancomycin TDM approaches. Third, a population pharmacokinetic analysis was conducted to explore the local population's vancomycin pharmacokinetic parameters and the influence of population-specific covariates on vancomycin plasma exposure.

### *1.7.1 Phase I (Retrospective chart review) specific objectives*

- i) To determine the appropriateness of routine vancomycin TDM service in Qatar, in relation to indication, sampling time, interpretation and subsequent dosage adjustment recommendations.
- ii) To evaluate the relationship between routine vancomycin TDM appropriateness and clinical outcomes.

### *1.7.2 Phase II (Prospective RCT) specific objectives*

- i) To compare the clinical outcomes between peak-trough-based and trough-only-based vancomycin TDM approaches.
- ii) To evaluate the relationship between vancomycin AUC/MIC ratios and cure.

*1.7.3 Phase III (Population pharmacokinetic analysis) specific objectives*

- i) To determine vancomycin population pharmacokinetics for Qatar and the influence of patient covariates on vancomycin pharmacokinetics and plasma exposure.
- ii) To evaluate the need for vancomycin dosing nomograms specific to Qatar's local setting and population.



## CHAPTER 2: LITERATURE REVIEW

### 2.1 Therapeutic drug monitoring (TDM): Definition and concepts

Therapeutic drug monitoring (TDM) utilizes patient-specific pharmacokinetic parameters to determine individualized drug dosage regimens, aiming to maximize pharmacotherapy outcomes and minimize toxicity ([46](#), [47](#), [77](#)). TDM is widely used for many drugs such as anti-epileptics, aminoglycosides, vancomycin, digoxin, and others ([46](#), [62](#)). Indications for TDM of selected drug classes vary ([46](#)). Depending on the relevant drug and patient case, serum drug concentration measurements may be ordered to rule out suspected toxicity, investigate suboptimal clinical response, design individualized dosage regimens for drugs with narrow therapeutic window, or assess patient adherence to drug therapy ([46](#)). However, in-vivo drug concentration measurements should be ordered only when an “appropriate” indication exists to avoid wasting expensive analytical tools and personnel time, thereby increasing economic burden on healthcare systems ([46](#), [62](#)).

Additionally, appropriate TDM services would potentially translate into improved health-care system efficiency and quality such as decreased personnel time utilization and the minimization of analytical tools needed due to inappropriate blood sampling ([46](#), [78](#)). However, the attainment of these documented multi-dimensional positive outcomes is dependent on the pre-analytical appropriateness of blood sampling time/technique as well as the correctness of post-analytical interpretation and clinical recommendation ([46](#), [47](#), [61](#), [62](#), [77](#), [79](#)).

### *2.1.1 The role of the pharmacist in TDM*

TDM is an essential tool in the pharmaceutical care process ([62](#), [79-81](#)). The American Society of Health-System Pharmacists (ASHP) statement stresses the importance of the clinical pharmacist's role in TDM to optimize patient-specific and healthcare system-specific outcomes ([80](#)). This role involves all stages of TDM continuum, including the decision of when to monitor drug levels and the evaluation of the clinical response to pharmacist-designed pharmacokinetic-based dosage adjustments. The latter statement concurs with the findings that pharmacist-provided clinical pharmacokinetic services significantly increased the number of serum drug concentrations that fall within the therapeutic range, the correctness of sampling time, serum creatinine monitoring, and post-analytical dosage adjustments ([82](#)). Similarly, pharmacist-run TDM services reported in other studies have been proven to significantly improve the appropriateness of TDM indication, pre-analytical sampling time and post-analytical clinical application ([57](#), [58](#), [70](#)).

### *2.1.2 Practical pillars for appropriate TDM service implementation*

In the context of TDM, the term 'appropriate' encompasses the appropriateness of all pre-analytical, analytical and post-analytical factors that impact the correctness and accuracy of the obtained drug serum levels and the subsequent clinician interpretation of findings and clinical recommendations ([46](#), [81](#), [83](#)). There are many factors that need to be considered in order to attain appropriate interpretation of reported serum drug levels and dosage regimen designs ([46](#), [47](#), [61](#), [62](#), [77](#), [79](#)). Initially, blood sampling should be conducted at an appropriate time (i.e. when steady state

levels have been achieved); peak concentrations are scheduled at the end of the distribution phase, while trough concentrations should be collected at the end of the dosing interval ([46](#), [47](#), [77](#)). This crucial pre-analytical factor requires an in-depth understanding of the absorption, distribution, metabolism and excretion (ADME) features of each drug and how patient disease states and potential food-drug, drug-drug, or drug-disease interactions may influence the time to steady state ([80](#)). In addition, correct interpretation of the reported serum levels should consider the patient's hepatic and renal clearance, comorbidities, body weight, co-medications, possible drug interactions, and other factors ([46](#), [80](#), [81](#)). Hence, sufficient knowledge of clinical pharmacokinetics principles and dosing adjustment is necessary to ensure appropriate pre-analytical sampling of blood, post-analytical interpretation of the drug levels and to guide appropriate dosing recommendations ([46](#), [61](#), [77](#), [81](#)).

## 2.2 Aspects of inappropriate TDM practices worldwide

Despite the reported positive clinical and economic impact of TDM, the application of TDM in the clinical setting remains at many times inappropriate worldwide, potentially hindering the attainment of the proven beneficial outcomes of TDM ([58](#), [71](#), [72](#), [84-90](#)). Many studies have reported that TDM practices were far from being completely appropriate; in relation to documentation quality of TDM requests, inappropriate indication for TDM, inappropriate sampling time, and inappropriateness of post-analytical interpretation and dosage adjustment recommendations. An extensive literature review was conducted to determine the TDM inappropriateness

practical aspects worldwide that would aid in designing a tool for the evaluation of the appropriateness of vancomycin TDM service in Qatar.

### *2.2.1 Significance to the current research project*

The explored and reported areas of deficient TDM practices vary across published studies. Given the similarity in TDM service principles across all TDM-monitored drugs, and in an effort to comprehensively capture the major inappropriate TDM practice aspects that need to be assessed in our project, the following literature review presented under section 2.2 was conducted. These aspects present barriers to the attainment of positive clinical and economic outcomes in disease states or clinical conditions that are treated with TDM-monitored drugs, including vancomycin. In addition, they represent potential confounders that are at many times overlooked when reporting the clinical and economic outcomes of TDM-monitored drugs such as vancomycin. The following sections (2.2.2 – 2.2.5) highlight deficient TDM practices worldwide that need attention and that will be part of our appropriateness assessment of vancomycin TDM service in Qatar. The sections serve as the literary work surrounding Phase I of this project, which has been conducted to assure that the “efficacy” reported in our project and other studies is observed in reality and translates to “effectiveness”.

### *2.2.2 Poor documentation quality of TDM requests*

TDM request forms must provide comprehensive information including indication for the request, sampling time, the timing of the last TDM drug dose, duration of therapy, the route of administration, the contact

information of the requester clinician, patient specific covariates (e.g. age, body weight, height, serum creatinine, etc.) and co-medications. Complete and quality documentation of all required data will ensure appropriate interpretation of reported serum drug concentrations and correct post-analytical clinical recommendations. This will prevent misinterpretation of findings and erroneous post-analytical actions that could lead to wastage of resources and therapeutic failures. The complete documentation on TDM request forms will potentially prevent the performance of an assay for an inappropriately collected blood sample and thus prevent waste of laboratory and human resources.

Many studies have reported poor documentation practices in TDM request forms, which hinder appropriate interpretations and subsequent clinician actions to drug levels ([61](#), [84](#), [86](#), [91](#), [92](#)). These practices represent inefficient TDM application, leading to potentially negative outcomes instead of the cost-savings and positive clinical outcomes that have been reported elsewhere ([61](#)). A retrospective regional audit, involving different clinical settings and specialties in Australia investigated the completeness of the documentation of 685 drug level request forms ([91](#)). The reviewed documentation parameters included: requester contact information, drug regimens, treatment duration, co-medications, indication and sampling time. The investigators reported that the appropriateness of the documentation of these parameters ranged from 6.4%-47.1%, with none of the request forms including complete documentation ([91](#)). Similarly, Irshaid et al. reported that out of 420 evaluated request forms in southwestern Saudi Arabia, more than 40% did not document the patient weight or indication for TDM, sampling

time, important covariates such as serum creatinine or albumin levels (84). Missing the documentation of sampling time is an alarming finding, since it is a major determinant of the post-analytical interpretation and dosage adjustments. Other less frequently undocumented information included patient age and gender, as well as the indication for which the patient is receiving the laboratory-monitored levels (84). Depending on the clinical diagnosis, target serum drug concentrations may vary (32). In New Zealand, an audit conducted by Sidwell and colleagues showed that drug dose and time were rarely documented in TDM forms, and the documentation rate did not exceed 14% of the assessed requests (86). However, the sampling time was documented in 84% of the forms (86). In India, incomplete documentation of TDM parameters was reported to hinder the analysis of 12% of the requests across four years (92). In addition, of 5094 TDM requisitions in another Indian tertiary hospital, 50% had incomplete documentation (90). The timing of sampling since last dose administration, the indication for TDM, and the duration of therapy were not filled in 22%, 20% and 15.5% of the TDM request forms, respectively (90). We noted that there were disparities in the documentation parameters reported by different studies, with only Sidwell et al. reporting the documentation of the requester contact details. A possible reason for the variability is the lack of consensus or guidelines on the structure and component of TDM documentation forms in clinical settings. Studies are needed to assess deficiencies in the documentation of TDM requests that would guide the design of complete TDM request forms, tailored to the needs of different clinical settings to maximize the appropriateness of documentation practices. In summary, there

is a need for standardized TDM request forms and documentation for quality assurance purposes and to ensure appropriate interpretation of serum drug concentrations and subsequent decision making on dosing.

Inappropriate documentation is not limited to missing/unfilled data, but also encompasses cases of ambiguous documentation. Despite the high rate of appropriate TDM practices in a tertiary hospital setting in Malaysia, Salih et al. found that the documented indications for TDM requests were ambiguous in most of the TDM requests they assessed (89). Two-thirds of the indications were stated as “check level” or “recheck level” (89).

The implications of these findings shall not be overlooked, as the practice of clinicians requesting drug levels without filling in their contact information is a potential barrier to effective communication between the laboratory personnel and the respective clinician. This factor may impact efficient timely communication between healthcare providers, especially in a world where the healthcare model is rapidly shifting towards multidisciplinary care. The availability of documentation about the interval between the last dose of the drug being monitored and the sampling time is needed so that the laboratory personnel can assure that the sample is appropriate before conducting the assay. Furthermore, complete documentation is an invaluable tool for quality assurance schemes and benchmarking processes, besides research. Thus, the features and structures of TDM request forms should be harmonized across practice settings in such a way that all required distinct data are unambiguously captured. Yet, the design of a standardized TDM request form does not absolutely guarantee high quality documentation. For example, in an Indian tertiary care setting,

well-designed standardized TDM order forms were used to capture patient information, medical information, and reason for the TDM order (92). Despite this, the investigators reported that incomplete TDM requests remained present, leading to misinterpretations of findings (92). Another potential reason behind inefficient documentation, that needs to be taken into account, is the incompetence of the involved clinicians and laboratory personnel. This has been confirmed by the finding that many of the hospital pharmacists in Qatar perceived themselves incompetent to provide clinical pharmacokinetic services (76).

### *2.2.3 Inappropriate indication for ordering serum drug concentrations*

Indications for TDM are variable and depending on the drug being monitored and the specific patient case, serum drug concentration measurements may be ordered to rule out suspected toxicity, investigate suboptimal clinical response, design individualized dosage regimens for drugs with narrow therapeutic window, or assess patient's adherence to drug therapy (46). However, TDM should be ordered only when an "appropriate" indication exists to avoid wasting expensive analytical tools and personnel time that could potentially increase the economic burden on healthcare systems (62).

Although TDM practice in developed countries was introduced during the last few decades, still inappropriate indications have been reported, possibly due to several reasons including inexperienced staff involvement (86). In their study, Sidwell et al. conducted an audit of 100 TDM orders for inpatients in New Zealand (86). Forty-seven percent of the



indications for TDM were potential for toxicity and ineffective treatment, while no clear indications were evident for 53% of the cases (86). In addition, more than 50% of the orders were for routine monitoring, requested unnecessarily with other routine laboratory investigations for inpatients. Routine monitoring remains one of the major causes of inappropriate TDM indication. In one study conducted in California, the authors found that of the 90 ordered TDM levels, only one TDM case led to a clinical action of dose adjustment in response to subtherapeutic concentrations, as most of the levels (38%) were ordered for routine monitoring (71). Similarly, another study found that the top reported reason for TDM orders was routine monitoring, which was not always appropriate (90). Interestingly, high rate of TDM requests (70%) has been found to be inappropriately indicated in Saudi Arabia (84).

On the other hand, studies from other settings reported higher rates of TDM indication appropriateness. In a Malaysian study involving three hospitals, higher indication appropriateness rates (77.4-82%) were reported (93). Similarly, high appropriate indications of TDM requests (98%) were reported in another setting in Malaysia with drug-drug interactions and inadequate response rated as most common appropriate indications, which may be attributed to the presence of a TDM pharmacist at their setting (89). In Malaysia, many pharmacy schools have extensive training on clinical pharmacokinetics and TDM in their curricula and as a result many tertiary hospitals have pharmacist-provided TDM services. A four-year retrospective audit of TDM in tertiary care settings in the Indian subcontinent involving 4359 requests was reported by Sharma and colleagues. The study reported

high rates of appropriate indication (92). These findings stress the needs for educational interventions to educate clinicians about appropriate TDM indications. Also, laboratory personnel need to be educated to assure that a correct TDM indication is present before a TDM request is processed, to prevent wastage of already limited healthcare resources.

#### *2.2.4 Sampling time inappropriateness*

Blood sampling should be conducted at appropriate timing (i.e. when drug steady-state levels have been achieved (46). This crucial pre-analytical factor requires an in-depth understanding of the ADME profile of each drug and how patient disease states and potential drug-food, drug-drug, or drug-disease interactions may influence the time to steady state (80).

Studies have reported that the sampling of blood for many TDM orders was conducted during the drug distribution phase, before steady state was achieved. More than 60% of the serum drug levels were obtained before steady state was reached and thus only a relatively small proportion of samples (19%) was appropriately sampled (84). In Switzerland, a retrospective analysis of 210 serum drug levels determined the appropriateness of sampling time (72). A large proportion of TDM cases (59%, n=125 samples) were inappropriate due to incorrect sampling time and most of those inappropriate samples were commonly ordered in response to inappropriate indication of routine monitoring, translating into preventable annual estimated costs of CHF 28,025 (72). Additionally, 17 (8.1%) drug levels were sampled during the distribution phase, which overestimates drug concentrations in drugs exhibiting multi-compartmental model

pharmacokinetics (72). Consistently, inappropriate sampling time was found to be present in up to 60% of 265 TDM requests in Malaysia (93). On the other hand, Sharma et al. found that blood sampling before steady-state attainment was reported in 6.9% of the cases investigated (90). Another study reported that pre-distribution phase samples were captured in 32% of the cases studied, resulting in 19% of the sera not reaching steady state (86). Despite the higher rates of appropriate TDM practices in another setting, sampling time remained an issue; whereby appropriate sampling time was reported in only 54% of the times, which was attributed to the high workload that might have hindered accurate timing of trough levels collection (89). These studies highlight a potential waste of resources (e.g. assays used, personnel working hours) and potential negative clinical consequences. However, the studies did not evaluate the clinical impact of inappropriate sampling time practices on clinical endpoint, which may warrant further research.

### *2.2.5 Inappropriateness of post-analytical interpretation and clinical recommendation*

Several factors need to be taken into consideration in order to attain appropriate interpretation of reported serum levels and dosage regimen designs (31). For instance, correct interpretation of the reported serum levels should consider the patient's hepatic and renal clearance, comorbidities, body weight, co-medications, possible drug interactions, and other factors. A study in Australia and New Zealand showed that minimal interpretation and clinical recommendations were provided to the ordered serum drug

concentrations (66). Surprisingly, most of the interpretations of antibiotics TDM results did not employ the methods recommended in the national clinical practice guidelines (66). Delattre et al. reported suboptimal interpretation of serum drug levels in Belgium (88). Likewise, despite that appropriate dosage adjustments are warranted when subtherapeutic levels are reported, this did not occur in 71% of the cases in New Zealand (86). In Malaysia, the presence of TDM clinical pharmacist may be a factor that led to the higher reported post-analytical actions in response to serum drug levels (60%); changes to patient management were employed in 60% of the cases post-analytically and were consistent with the clinical pharmacist's recommendations in 76% of the cases (89). In addition, the respective clinical context should be considered during the interpretation of serum drug levels. First, the appropriateness of the chosen drug and the dose should be taken into account. In one study, a poor correlation between suspected toxicity and supra-therapeutic drug levels was found in 19% of the TDM cases (86). A possible reason may be that clinicians ordered TDM secondary to unspecific toxicity symptoms that were widely pertinent in the general inpatient comorbid population.

#### *2.2.6 Incompetency of TDM service providers*

The high prevalence of inappropriate TDM post-analytical actions, including misinterpretations and inappropriate dosing recommendations may be attributed to educational background and training of TDM service providers. It was reported that a wide range of professionals such as clinical chemists, clinical pharmacologists, pathologist, microbiologists, pharmacists,

and medical staff contributed to the provision of TDM services (66, 76). A recent study conducted by Kheir et al. explored the perceived barriers to the application of clinical pharmacokinetic services by hospital pharmacists in Qatar (76). The study enrolled 112 pharmacists working at seven hospitals under the Hamad Medical Corporation (HMC), the major healthcare provider in Qatar (76). The hospital pharmacists reported that they spent most of their duty hours in technical tasks (e.g. inventory issues, technical dispensing roles), as compared to cognitive functions (e.g. applying clinical pharmacokinetic knowledge). The majority of hospital pharmacists (74.4%) reported that most of the times they did not utilize their clinical pharmacokinetics knowledge in practice. More importantly, approximately 70% of the respondents considered their clinical pharmacokinetics skills inadequate to provide optimal application in the clinical setting. Poor understanding of clinical pharmacokinetics principles by pharmacists and clinicians were found to be important barriers to the application of clinical pharmacokinetic services in the current setting in Qatar (76). These important findings signify that potential means of optimization vancomycin TDM services in Qatar exist, as studies have shown that pharmacist-provided TDM services significantly improved clinical outcomes and TDM appropriateness (57, 58, 70). Measures should be taken such that more clinical pharmacists are trained and involved in leading and directing TDM services to attain the fruitful outcomes of TDM. Part of these measures is the assessment of the appropriateness of TDM services application in many unstudied settings such as Qatar, to determine the areas of clinical pharmacokinetics knowledge deficiencies that are specific to the local pharmacists.

### *2.2.7 The use of non-population specific dosing nomograms*

Another potential factor that may lead to suboptimal post-analytical dosage recommendations is the application of imported dosing nomograms to other populations. A study conducted in India reported that more than 30% of serum drug levels were out of the therapeutic window, signaling possible ethnic and inter-individual variability (92). In Kuwait, initial antibiotic dosage estimation using five nomograms resulted in insufficient dosing of 63% of the patients studied (94). Based on that, clinical pharmacokinetics studies specific to unstudied ethnic groups and races are highly advocated. Population pharmacokinetic modeling and simulation studies are invaluable for establishing dosing nomograms and monitoring recommendations in different populations (95). The establishment of good pharmacokinetic population models by the inclusion of population-specific covariates result in minimizing inter-subject variability (95). Extrapolating and applying published population-based dosing nomograms to other populations does not guarantee their clinical utility to maximize efficacy and minimize toxicity (96). For example, a study evaluated the predictive performance of several published population pharmacokinetic vancomycin models into their setting and found that not all the models applied to their population, and that only models derived from populations with similar covariate distributions to their population showed good predictive performance (97).

## 2.3 Therapeutic drug monitoring of vancomycin

### *2.3.1 Introduction to vancomycin TDM*

TDM of vancomycin is an integral part in ensuring the attainment of positive clinical outcomes (efficacy) and minimizing adverse events associated with the drug including nephrotoxicity (safety) (31). Studies have highlighted AUC divided by MIC as vancomycin pharmacokinetic-pharmacodynamics (PK-PD) index that is associated with microbiological and clinical outcomes (53). The 2009 IDSA guidelines for MRSA pharmacotherapy recommend a vancomycin goal of  $AUC_{24}/MIC \geq 400$ , based on the findings of Moise-Broder and colleagues (49). Moise-Broder et al. reported superior clinical outcomes when vancomycin treatment achieved  $AUC_{24}/MIC \geq 400$  (p-value < 0.005) in 108 patients with staphylococcal lower respiratory tract (LRT) infections, which translated into shorter time to bacterial eradication (10 vs. 14 days) and substantial clinical success (49). This study has its limitations, being restricted to only patients with pneumonia, calling into questions the generalizability of this ratio to other infection sites. Years later, other studies reported different AUC/MICs vancomycin cure breakpoints (53). Additionally, controversies regarding the best vancomycin TDM approach (i.e. trough-only-based versus peak-trough-based approaches) that is associated with better AUC/MIC vancomycin breakpoints for cure remain unanswered in the published literature. The following sections will discuss the major controversies regarding optimal dosing and TDM approaches of vancomycin, which are the focus areas of this project.

### 2.3.2 Clinical benefits of vancomycin TDM

Studies have been conducted to assess the clinical benefits of vancomycin TDM; patients who received vancomycin TDM showed superior clinical outcomes, less utilization of cumulative vancomycin, shorter durations of vancomycin therapy as well as less hospitalizations when compared to those who did not ([39](#), [60](#), [98-100](#)). A common feature amongst these studies is that they were all published before the release of the 2009 IDSA vancomycin TDM guidelines, which suggests that the traditional vancomycin TDM approach was the method utilized in those studies. Of those, the only RCT was in Spain, which was conducted to determine the cost-effectiveness of vancomycin TDM in immunocompromised hematologic malignancy patients ([98](#)). The clinical pharmacist utilized pharmacokinetic principles to individualize vancomycin doses in the TDM group (n=37), while the control group (n=33) did not receive the vancomycin TDM service ([98](#)). Compared to the TDM-arm, the control arm experienced higher incidences of minor nephrotoxicity by 2.5 folds ([98](#)). Logistic regression showed that vancomycin TDM independently decreased the rates of moderate nephrotoxicity [non-TDM group: 9.1% vs. TDM-group: 0%] ([98](#)). Thus, vancomycin TDM resulted in incremental cost-avoidance of \$435 per case of nephrotoxicity ([98](#)). Nevertheless, no differences in the global clinical outcome was found between both arms ([98](#)), which can be attributed to the small sample size, meaning that the study was underpowered to detect an effect. In Japan, a retrospective evaluation of 184 MRSA infected patients showed a statistically significant decline in renal function in the non-TDM cohort compared to the TDM-cohort ([99](#)). In addition, patients achieving



vancomycin peak concentration targets required significantly less mean duration of vancomycin treatment which resulted in the receipt of significantly less vancomycin cumulative doses by approximately 10g (99). Given the retrospective design of the study, the quality of vancomycin TDM service is a potential confounder that should have been assessed since it could have contributed to underestimating the magnitude of the positive clinical outcomes of vancomycin TDM. Similar findings were reported by a prospective cohort study in a tertiary care hospital in USA (60). Patients receiving vancomycin TDM showed less renal adverse effects, less cumulative vancomycin doses received by 5g, and mean length of hospitalization less by approximately one week compared to the vancomycin treated patients who did not receive the TDM service (60). However, other efficacy measures were similar between the two cohorts (60). Again, a possible explanation is that vancomycin TDM quality was not accounted for, which could have contributed to underestimating the difference in the efficacy measures. The positive clinical impact of vancomycin TDM prove it as an important intervention that if used efficiently, would result in health-care associated cost-avoidance and minimization of the emergence of VISA strains.

Despite the positive outcomes earlier discussed, controversies in the literature remain regarding the impact of vancomycin TDM on overall clinical effectiveness (60, 98, 100). A study including 79 patients in Japan proved the higher clinical effectiveness rate in vancomycin TDM subjects (75%, n=48), with approximately half of non-TDM managed patients not achieving clinical effectiveness with vancomycin treatment (48%, n=31)

(100). A possible explanation to ineffectiveness of vancomycin treatment in 25% of the patients who received vancomycin TDM is that the dosage adjustment method was not based on achieving the AUC/MIC target in 35.4% of these cases (100). Other studies failed to detect significant differences in some effectiveness measures between vancomycin treated patients who received TDM versus those who did not (60, 98). The results published by Mochizuki and colleagues in 2010 add to this controversies; their retrospective evaluation of 20 patients receiving vancomycin treatment for catheter-related bacteremia showed that patients who received vancomycin TDM had less efficacy and more nephrotoxicity compared to non-TDM patients, although these were statistically non-significant (101). This study is the only study that reported the complete non-superiority of vancomycin TDM, and it is the only study published after the release of the 2009 IDSA guidelines suggesting that they might have utilized the trough-only approach. In addition to the small sample size, the authors did not appraise the appropriateness of the TDM service, both of which are major limitations to the validity of the reported findings.

To address the controversy surrounding the necessity of vancomycin TDM, a recently published meta-analysis confirmed that vancomycin TDM was associated with higher clinical efficacy and less nephrotoxicity (39). Yet, the examiner of the literature observes the paucity of studies examining the clinical outcomes of vancomycin TDM. Most of the studies have methodological weaknesses, which include observational designs as well as small sample sizes (39). The most important limitation noticed across most of the studies is that no appraisal of the appropriateness and quality of the

provided vancomycin TDM service was conducted, prior to evaluating the clinical outcomes. The extent of appropriateness of vancomycin TDM service is a major confounder that could explain this controversy, and the observed suboptimal outcomes with vancomycin TDM in some settings. Thus, vancomycin TDM service appraisal studies that are specific to different clinical settings are needed to address this gap in the literature.

Most of the studies reporting the positive outcomes of vancomycin TDM were published before the release of the 2009 IDSA guidelines, which indicates the use of traditional vancomycin TDM approaches utilizing peak and trough concentrations measurement ([60](#), [98-100](#)). The study reporting failure of TDM was published in 2010, a year after the release of the 2009 IDSA guidelines which suggests they were possibly utilizing trough-only vancomycin monitoring recommended in the IDSA guidelines ([101](#)). Overall, these findings suggest that vancomycin TDM approach is a potential driver of the outcomes. To the best of our knowledge, no prospective head-to-head comparisons were reported in the literature to address this question.

### *2.3.3 Suboptimal clinical outcomes associated with vancomycin treatment*

Despite the proven clinical efficacy when appropriately used, suboptimal clinical outcomes remain observed in the clinical setting when vancomycin treatment is used, suggesting inadequacy of vancomycin current dosing and monitoring practices. A study reported that mortality rates in *S.aureus*-related bacteremia (SAB) were significantly higher in vancomycin-treated patients compared to those treated with beta-lactams. The authors reported that more than half of the subjects had troughs less than 10 µg/mL

and thus, they attributed the high mortality rates to the low vancomycin exposure rather than high MIC (34). Despite MRSA not found to be an independent risk factor for death (19), mortality rates have been reported to be more than 20% (28). A multicenter cohort of 372 patients showed that MRSA infection was not an independent risk factor for mortality (19). Yet, outcomes of MSSA bacteremia treated with vancomycin have been associated with mortality compared to beta-lactams. Moreover, vancomycin treatment failure has recently been found to be predicted by the site of infection rather than the MIC (42). This indicates the probability of different infection sites achieving variable vancomycin penetration levels, which questions the adequacy and generalizability of the current vancomycin dosing and monitoring practices in achieving optimal infection site exposure across different disease states. In IE patients treated with vancomycin, bacteremia persistence was attributed to the slow eradication effect of vancomycin, suggesting inadequate in-vivo vancomycin exposure (5). However, the authors did not report the dosing and monitoring practices of vancomycin. In a 532 Australasian cohort of SAB, the association between the choice of antibiotic treatment and 30-day mortality was explored; the increase in vancomycin MIC was associated with more mortality even in patients who did not receive vancomycin (41). These findings suggest that the clinical failures with vancomycin treatment may be related to suboptimal plasma exposure to vancomycin. None of these studies appraised the quality of the provided vancomycin TDM services as a potential factor towards suboptimal vancomycin plasma exposure.

The epidemiology of inadequate antimicrobial therapy remains a

significant factor for mortality in clinical settings. Approximately 30% of ICU patients received inadequate antimicrobial treatment for their bloodstream infections (102). The most common pathogens associated with suboptimal antimicrobial treatment included oxacillin-resistant *S.aureus* (ORSA) (n=46; 32.6%) and coagulase-negative staphylococci (n=96; 21.9%) (102), to which vancomycin is considered the mainstay of treatment. Longer duration of mechanical ventilation, [mean difference = 4.2 days, p-value<0.001], total length of hospital stay [mean difference = 6.4 days; p-value=0.10], and ICU stay [mean difference = 4.3days; p-value<0.001] were observed in critically-ill subjects receiving suboptimal antimicrobial management compared to those receiving adequate therapy (102). More importantly, inadequate antimicrobial therapy was identified as the major risk factor for death in ICU patients with bacteremia (102). According to a multivariate analysis, suboptimal antimicrobial management in critically-ill subjects with blood stream infections is associated with about 7 times higher risk of death [aOR=6.86; 95% CI: 5.09-9.24; p-value<.001] (102). Moreover, suboptimal antimicrobial management was associated with negative clinical sequelae, including systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock and multiple organ failure (102). Despite the fact that methicillin resistance is not an independent risk factor for death (9), death trends were significantly higher in MRSA IE compared to MSSA IE [50% versus 9.1%; p-value=0.019], signifying inadequacy of antimicrobial treatment (11). In contrast, no significant association was found between higher mortality rates and persistent bacteremia (11). Thus, strategies aimed at increasing the adequacy of

vancomycin treatment to achieve target plasma exposure will reflect in significantly better clinical outcomes and less costs. The provision of initial sufficient antibiotic management and appropriate adjustments post-initiation in patients with MRSA was found to be an independent protective factor (19). To date, optimal dosing and TDM practices of vancomycin are hot topics of research and continuous debate.

The prevalence of inadequacy of vancomycin treatment is more profound in Asia, including MENA. According to a recently published meta-analysis of 91 studies reporting the epidemiology of VISA and HVISA isolates between 1997 and 2014, the trend of VISA epidemiology has increased, with higher incidence rates in Asia compared to other continents (i.e. Europe and USA (14). This trend is therefore a global health concern. Given that suboptimal antimicrobial therapy of MRSA contributes to the emergence of isolates of higher MIC, these findings highlight the high prevalence of inadequate vancomycin treatment in the Asian region, including the MENA. The inadequacy of vancomycin treatment in Asia can be attributed to the limited generalizability of vancomycin PK-PD targets reported elsewhere, since differences in MRSA clones between Asia and USA populations have been reported (10). Another factor towards the suboptimal achievement of vancomycin targets in the Asian region is the inappropriateness of TDM practices that has been widely reported (43). There is paucity of studies exploring these factors, with none conducted in Qatar.

#### *2.3.4 Inappropriate vancomycin TDM practices*

In section 2.2, we have discussed inappropriate TDM practices globally in general. The discussion in this section focuses on inappropriate TDM practices related to vancomycin. High prevalence of inappropriate vancomycin utilization, dosing and monitoring practices has been reported, which could contribute to the clinical failures reported with this drug worldwide ([45](#), [56](#), [99](#), [103-109](#)). In Japan, a retrospective evaluation of 184 MRSA infected patients showed that the majority (n=111; 60.32%) of vancomycin treated patients did not receive vancomycin TDM ([99](#)). Similarly, an evaluation of 117 glycopeptide treatment cases across multiple hospitals in France showed that 22% of the cases did not receive adequate TDM with only 1.7% of all cases satisfying all appropriateness criteria; dose adjustments secondary to non-therapeutic glycopeptide concentrations occurred minimally (32%) ([44](#)). In a similar setting, appropriate TDM was done in only 40% of the reviewed glycopeptide cases ([106](#)). Another retrospective evaluation of 2,597 vancomycin blood specimens collected over 13 months revealed that 41.3% of the specimens were sampled earlier than the correct timing, leading to falsely elevated vancomycin serum concentrations, resulting in erroneous clinical actions which included under-dosing patients or discontinuing the medication ([103](#)). Furthermore, incorrect timing of vancomycin blood specimens collection resulted in clinicians reordering the specimen in 29.2% of the times, which imposes avoidable cost burden to the healthcare system ([103](#)). Elsewhere, out of 64 assessed vancomycin specimens, the majority (94%) were inappropriate ([56](#)). A cross-sectional study conducted by Davis et al. across different hospitals in

the US confirmed the inconsistency and inappropriateness in the sampling time of vancomycin trough concentrations, indicating non-adherence to clinical pharmacokinetic principles and the 2009 consensus guidelines (109). In line with these findings, inappropriate dosage adjustments were observed in 50% of patients with vancomycin-related decrease in renal function in a teaching hospital in Iran (107). In Oman, Al Za'abi and colleagues retrospectively evaluated vancomycin use in patients hospitalized in a university teaching hospital (110). Inappropriate vancomycin TDM practices were reported including dose adjustments not implemented in 70% and 34% of subtherapeutic and supratherapeutic vancomycin serum concentrations, respectively (110). Discrepancies in the TDM approach were noticed, whereby both peak-trough monitoring and trough-only monitoring approaches were utilized in the setting (110). Correspondingly, high rates of inappropriate vancomycin TDM practices were reported in relation to inadequate dosing, sampling before steady-state attainment, and sampling outside the trough time window (111). Other studies reported suboptimal use of vancomycin treatment in their settings which corroborate with these findings (45, 105). Undoubtedly, these reports of inadequate vancomycin dosing and monitoring practices highlight non-compliance to evidence-based clinical practices and represent major sources of vancomycin treatment failures that warrant setting-specific investigations.

### *2.3.5 Controversies regarding the optimal AUC/MIC ratio for vancomycin*

Published evidence exists that extensively queries the 2009 recommended target ratio ( $AUC/MIC > 400$ ) (28, 34, 53). A recent study in



critically-ill patients with MRSA bacteremia and MRSA osteomyelitis reported an AUC/MIC breakpoint of 293, that was associated with the largest significant difference in time to microbiological clearance, reflecting into statistically significant reduction in mean time to microbiological cure by 48 hours compared to AUC/MIC<293 [4±2 versus 6±3 days; p-value<0.01] and MRSA related hospitalization by 5 days [13±6 versus 18±14 days; p-value=0.25] (28). Recurrent bacteremia resulting in re-hospitalization was 17% versus 39%; p-value=0.09 in patients with AUC/MIC ratio of >293 and ≤293, respectively (28). In line with this breakpoint, Brown et al. reported a similar vancomycin AUC<sub>24</sub>/MIC ratio of 211 in subjects with complicated MRSA bacteremia and IE that was a statistically significant independent predictor of death; AUC<sub>24</sub>/MIC ratio < 211 was associated with more than 4 times higher rates of mortality versus subjects who achieved AUC<sub>24</sub>/MIC ratio>211 (34). Jeffres et al. investigated whether AUC and trough levels of vancomycin were associated with death in subjects with hospital-acquired pneumonia due to MRSA (n=102) hospitalized over 6.5 years (112). Per stratification of the cohort AUC values and vancomycin trough levels, no statistically significant difference (p>0.8) was observed in vancomycin pharmacokinetic indices between survivors (AUC: 351±143 µg/hr/mL; trough: 13.6±5.9 µg/mL) and mortality events [AUC: 354±109µg/hr/mL; trough 13.9±6.7 µg/mL] (112). Despite the inclusion of pneumonia only patients, lower vancomycin AUC breakpoints were reported when compared with Moise-Broder's study (49). Interestingly, the 2009 IDSA-ASHP recommended trough levels were achieved in some of the patients, but this did not reflect in less mortality. This questions the appropriateness of

utilizing trough-only monitoring as a surrogate for the attainment of optimal AUC/MIC vancomycin cure breakpoint, suggested by the 2009 IDSA-ASHP consensus guidelines. It is important to note that heterogeneity in genetic composition of *S. aureus* strains has been reported (41, 52), which may explain the variable AUC/MIC ratios reported. Strain-specific characteristics of staphylococcal bacteria impact the clinical outcomes in patients treated with vancomycin (51). These features of bacteria strains may differ across continents (50), and thus extrapolation to our setting is controversial. Additionally, a possible cause of the different reported AUC/MIC ratios is the different laboratory methods (Etest vs. microdilution) of MIC determination across different settings/studies (28), limiting their generalizability and warranting setting-specific calculations. In general, these studies suggest that optimal vancomycin AUC/MIC target for cure differs across different populations, type/site of MRSA infections, bacteria-specific genetic and virulence make-up. This warrants population and setting-specific investigations.

#### *2.3.6 The traditional approach: Peak-trough-based vancomycin TDM*

Traditionally, vancomycin TDM comprises of measuring both peak and trough serum concentrations at steady state for the determination of individualized pharmacokinetic parameters, and if warranted, dosing adjustments. The inclusion of peak concentrations in vancomycin TDM practices remained the standard of practice until some studies concluded that no association exists between vancomycin peak concentrations and clinical efficacy and toxicity outcomes. Conventionally, vancomycin was described

to possess both concentration-dependent and time-dependent effects, advocating the monitoring of both steady state peak and trough drug serum levels to assure clinical efficacy and prevent nephrotoxicity; this dosing approach targets a  $C_{\text{peak}}$  of 20–40  $\mu\text{g/mL}$  and a  $C_{\text{trough}}$  of 5–10  $\mu\text{g/mL}$ (31). In-vitro and animal studies proved that vancomycin possesses concentration-dependent bactericidal activity if *S.aureus* MIC is less than 1.5 mg/L, with time-dependent killing associated with higher MICs (113). No association was detected between time above MIC and infection cure (49). The fact that vancomycin penetrates in low amounts (25% of the serum levels) into the lung tissues and exhibits huge inter-individual variation may explain this finding (114). Hence, this finding cannot be generalized to all disease states, as it came from a study that included patients with LRT infections only. The first study in humans suggesting that vancomycin peak monitoring is not required was by Suzuki et al. in which significant differences in troughs and AUC/MICs were seen between patients who experienced clinical efficacy or nephrotoxicity (115). Suzuki's group reported that  $C_{\text{max}}$  did not significantly differ between patients who experienced nephrotoxicity versus others. Based on that,  $C_{\text{min}}$  monitoring is considered to be sufficient in order to reduce cost. The study has several limitations including small sample size, retrospective design and restricted to only patients with pneumonia (115). This can be explained by the huge interindividual variability between peaks and thus, a link could not be found even if it exists (48). Saunders measured post-dose vancomycin concentration elevations in 165 paired samples taken from adult subjects not requiring renal replacement therapy, reporting that as long as troughs are below 15 $\mu\text{g/mL}$ , peaks (measured 60 minutes after infusion) will

remain in the safe ranges and hence need not to be monitored (113). This means that any trough level above 15µg/mL does not guarantee a safe peak level, a finding that contradicts the current guidelines recommended troughs above 15 µg/mL.

Evidence strongly advocates the potential superiority of the traditional peak-trough-based vancomycin TDM compared to the 2009 recommended trough-only-based TDM approach. A retrospective study involving 184 patients with MRSA had proven a probable association between vancomycin peak monitoring and clinical efficacy (99). Compared to the non-TDM group, peak monitoring resulted in less total doses of vancomycin needed and superior clinical efficacy with less nephrotoxicity. More importantly, patients with peaks above 25 mg/L showed significantly shorter duration of treatment by 13 days compared with peaks less than 25 mg/L. Decreasing the amount of cumulative doses needed would potentially result in lower antibiotic resistance rates and lower cost. Nephrotoxicity attributable to vancomycin monotherapy was in 5% of the cases and is mostly related to serum peaks exceeding 40 mg/L (113). Irreversible deafness rarely occurs and is associated with extremely elevated levels (>80 mg/L) (116). A recently published study by Hong and colleagues brings victory once again to the utility of peak-trough-based vancomycin TDM (117). The outcome assessed was the achievement of target serum drug concentrations at steady-state (C<sub>ss</sub>), which was higher in the peak-trough group (prospective cohort, n=75) compared to the trough only approach (retrospective cohort, n=75) [65.3% vs. 31%, p-value<0.05] (117). These findings are consistent with the results of the largest most recent prospective

study by Neely and colleagues who analyzed 569 vancomycin levels from subjects taking single or multiple vancomycin doses of 400-1400 mg, across a comprehensive range of estimated creatinine clearance (CrCl: 6.4-174.7 mL/min) (48); the investigators compared AUCs obtained from trough-only ( $AUC_T$ ) and peak-trough ( $AUC_{PT}$ ) models to the AUC obtained from the full model ( $AUC_F$ ). The full model was built from an independent data set that consisted of richly sampled concentrations in addition to the peaks and troughs. The  $AUC_{PT}$  more precisely and accurately estimated the  $AUC_F$  with less variability ( $R^2=0.94$ , median residuals [IQR]: -139.6 [-958.7-1,468.0]), versus  $AUC_T$  ( $R^2=0.7$ ; median residuals [IQR]: -97.1 [-2,625-2,478]). The peak-trough model as well as the trough-only model underestimated the AUC compared to the full model. The AUCs calculated from peak-trough ( $AUC_{PT}$ ) as well as trough-only ( $AUC_T$ ) data were significantly less than the complete data set ( $AUC_F$ ) per subject (rich sampling), with the peak-trough model showing better estimates; the median  $AUC_F$  was more than  $AUC_{PT}$  by 159.3 [95% CI: 63.6-284.6;  $p$ -value <0.001]; median  $AUC_F$  was more than  $AUC_T$  by 341.9 [95% CI: 189.8-553.4;  $p$ -value<0.001]. These findings advocate the combination of population-pharmacokinetic methods and peak-trough-based approaches to optimizing vancomycin dosing and monitoring practices in unexplored settings and populations.

### 2.3.7 The IDSA 2009 guidelines approach: Trough-only-based vancomycin TDM

Trough-only-based vancomycin TDM was recommended by the 2009 IDSA-ASHP guidelines to attain AUC/MIC ratio of  $\geq 400$ ; the target surrogate to attain efficacy (32). Based on limited human data and animal

studies showing that vancomycin is “concentration-independent”, vancomycin peak concentration monitoring was not recommended (32). Additionally, Since it is hard in the clinical settings to obtain several vancomycin serum concentrations to calculate the AUC, the IDSA-ASHP guidelines recommended that trough levels prior to the fourth dose (i.e. when steady state is likely reached) are monitored as a surrogate for achieving  $AUC/MIC > 400$ . To achieve treatment cure and prevent the rising resistance in mild to moderate infections, trough vancomycin levels should be kept above  $10 \mu\text{g/mL}$ . Target trough levels are recommended to be  $15\text{--}20 \mu\text{g/mL}$  to achieve an  $AUC/MIC$  ratio of  $\geq 400$  in severe invasive infections; namely MRSA bacteremia, pneumonia, endocarditis, meningitis, and osteomyelitis. Before the 2009 guidelines, the traditionally recommended trough vancomycin level was  $5\text{--}10 \mu\text{g/mL}$ , which was purely theoretical; this trough was based on the susceptibility  $MIC < 5 \text{mg/L}$  for organisms treated with vancomycin (113). Positive clinical outcomes pertinent to maintaining these high trough levels have not been explicitly proven yet (42). Patients with vancomycin serum levels of  $15 \mu\text{g/mL}$  had higher likelihood to have heart failure, kidney insufficiency, as well as requirement of ICU care versus those with lower troughs with no significant differences in treatment failures (118). On the contrary, evidence has proven that dosing regimens targeting troughs more than  $15 \mu\text{g/mL}$  result in incidences of acute kidney injury (AKI) (119). Furthermore, most of these recommendations were not based on prospective randomized trials; the level of evidence was mostly III B (i.e. evidence from opinions of respected authorities, based on clinical experience,

descriptive studies, or reports of expert committees), and the grades of recommendations are mostly moderate.

The use of vancomycin trough level as an indicator of AUC/MIC optimal exposure is greatly criticized as reported findings showed that using troughs as surrogates for AUC/MIC ratio is unacceptable and that patients' AUCs need to be calculated (55, 120). This discrepancy is scientifically and theoretically valid and has been proven in the literature, raising criticism to the 2009 IDSA-ASHP practice guidelines. The use of trough levels were only useful to explain approximately 40% of the huge inter-individual variability in vancomycin AUC (48, 54, 55); trough-only monitoring under-predicts AUC on average by 25% when patient-specific factors are not accounted for. This raises concerns on the adequacy of trough-based monitoring in patients with various physiologic and renal states (48). Contradicting the 2009 consensus guidelines, vancomycin levels were not found to correlate with AUC<sub>24</sub>/MIC in patients diagnosed with MRSA bacteremia and osteomyelitis (28). Similarly, multivariable logistic regression analysis did not prove C<sub>min</sub> ≥15µg/mL as an independent predictor of AUC<sub>0-24</sub>/MIC target attainment (121). As the AUC is a measure of cumulative drug exposure during a certain timeline, it is not surprising that a single point measurement at the end of the dosing interval (i.e. trough level) represents a poor estimate of the AUC. Based on that, the recommended vancomycin trough concentrations within the range of 15–20 µg/mL do not necessarily imply optimal AUC/MIC exposures in patients especially with high MIC values (> 1µg/ml). Out of 5000 simulations, achieving the PK-PD target of AUC/MIC>400 for MIC of 1 µg/mL required troughs less than the recommended by the 2009 IDSA

guidelines (i.e. 15 µg/mL) for serious infections, meaning that optimal exposure may be achieved with lower troughs and thus less nephrotoxicity. These multiple studies prove that the current trough-only-based vancomycin monitoring and subsequent dosing adjustment is a debatable practice and needs to be revised. Calculating AUC in practice is cumbersome and impractical, as it requires multiple collections of blood samples per patient per dosing interval. Thus, studies are needed to explore better approaches to estimate and achieve target vancomycin AUC/MIC in practice without the need for multiple sampling per dosing interval.

#### *2.3.8 Limited external validity of published vancomycin dosing nomograms*

As extensively discussed in the previous section (2.3.7), current evidence calls into question the appropriateness, adequacy and safety of the 2009 guideline recommended dosing to achieve the target troughs of 15–20 µg/mL. Insufficient dosing would result in serum concentrations less than 10 µg/mL, which may potentially result in increased MIC and resistance ([122](#), [123](#)). Increasing MIC of MRSA has been reported, requiring more aggressive dosing and higher troughs ([124](#)). Conversely, vancomycin treatment failure has been recently found to be predicted by the site of infection rather than MIC ([42](#)). The multinational DALI cohort study explored the adequacy of the current vancomycin dosing in ICU at achieving the goal PK-PD index (AUC/MIC>400), using data from 42 patients obtained from 26 ICU units across 8 countries ([121](#)). Trough levels showed high inter-individual variability [median (IQR): 27(8-23) µg/mL], with target troughs and AUC<sub>0-24</sub>/MIC ratio only achieved in 57% and 50% of the patients, respectively,



assuming MIC=1µg/mL(121). For MICs ranging from 0.5 to 2 mg/L, PK-PD target would be achieved in 38% of patients (121). In patients with normal creatinine clearance in China, troughs 15-20 µg/mL were achieved with vancomycin doses that were significantly less than the guideline recommendations. Contrariwise, in patients with creatinine clearance less than 70mL/min, the target of 15-20 µg/mL was achieved with significantly higher doses than the recommended (125). Another prospective cohort study challenged the adequacy of the guideline recommended dosing (minimally 15 mg/kg/dose) in patients with MRSA bacteremia aged at least 65 years old, as 40% of the patients achieved troughs below the 15mg/L (126). A prospective study showed that with the current vancomycin suggested dosage regimens, more than 90% of the patients' trough levels did not achieve the target (15-20 µg/mL) and that 54.3% had troughs less than 10 µg/mL (127). Using consecutive Monte Carlo simulations, and only using data from subjects who achieved troughs of 15-20 µg/mL, Patel et al. reported that the likelihood of achieving the target of  $AUC/MIC \geq 400$  was 57% with the highest dose possible (2 g every 12 h) when MIC is 2 µg/mL, while increasing nephrotoxicity risk by more than 30% (55). When the MIC is 1 µg/mL, total daily vancomycin doses more than 3g showed more than 80% probability to achieve the target serum levels but exerted intolerable nephrotoxicity risks (55). Also, despite receiving doses per the 2009 IDSA-ASHP consensus guidelines (15 mg/actual body weight, maximum 2 g/dose), 91% of vancomycin treated patients were not able to achieve  $AUC/MIC > 293$ , in a study showing this ratio as the breakpoint for efficacy (28). Similarly, despite the TDM requests increasing 12-fold over three years in

Saudi Arabia, vancomycin trough monitoring did not change the rates of subtherapeutic levels, while the rates of nephrotoxicity has increased, questioning the generalizability of vancomycin dosing and monitoring guidelines to the MENA region and population (128). Moreover, the recommended vancomycin dosing per 2009 IDSA-ASHP guidelines (average 16mg/kg/day) resulted in AUC/MIC <211, the breakpoint for efficacy, while exceeding this breakpoint required an average daily dose of 22mg/kg/day (34). Interestingly, vancomycin-related nephrotoxicity has been reported in 10–20% of subjects on conventional vancomycin doses versus 30–40% of subjects on higher vancomycin doses that are suggested by the 2009 IDSA guidelines (129). In North West China, authors reported 15.6% cases of nephrotoxicity from 90 critically ill patients (130). The mean vancomycin trough concentrations were less than the therapeutic range recommended by 2009 IDSA-ASHP guidelines in both cohorts without statistically significant differences detected between nephrotoxicity cases (n=14) versus controls (n=76) [14.5±6.3 versus 10.7±4.9 µg/mL; p-value=0.184]. Interestingly, it was noted that these patients required mean vancomycin doses (30.6-34.9mg/kg/day) that were higher than those recommended by the 2009 IDSA-ASHP guidelines, to achieve the reported subtherapeutic trough concentrations (130). In another study, nephrotoxicity has been reported in 43% of the patients who had their trough levels within the 2009 IDSA-ASHP recommended targets (i.e. less than 20 µg/mL) (28). Aggressive dosing regimens and longer treatment durations with vancomycin may be potential risk factors for nephrotoxicity (130, 131). Collectively, these studies stress the need for contemporary vancomycin dosing and monitoring reevaluation in

different populations, settings and disease states as it seems that a one-size-fits-all dosing is not always optimal for vancomycin TDM.

The 2009 guidelines were predicated mainly on the creatinine clearance of patients, leaving many population-specific covariates to be explored (132). Population pharmacokinetic modeling and simulation studies are invaluable to establishing dosing nomograms and monitoring recommendations in different populations (95). The establishment of good population pharmacokinetic model by the inclusion of population-specific covariates results in minimizing inter-subject variability (95). Studies have identified that covariates such as cystatin C and albumin levels are associated with vancomycin levels (133), and that trough levels monitoring alone is not adequate to achieve optimal dosing (48). Simulations of doses enables the determination of vancomycin doses that result in higher probability of achieving optimal AUC/MIC (134). In a study involving 596 patients in Korea, Jin et al. reported that the calculated AUC based on CrCl was significantly lower than the AUC based on patient-specific PK parameters [392.38 vs. 418.32 mg·hr/L, p-value<0.0001] and that the former showed weaker correlation with trough concentrations (r=0.649 vs. r=0.964) (135). Therefore, creatinine clearance tends to underestimate vancomycin clearance and population-specific parameters should be factored in these determinations. Extrapolating and adapting published population-based dosing nomograms to other populations is not always a guarantee that they are suitable to maximize efficacy and minimize toxicity (96). For example, a study evaluated the predictive performance of several published population pharmacokinetic vancomycin models in their population and found that not

all models applied to their population, and that only models derived from populations with similar covariate distributions to their population showed good predictive performance (97). The design and utilization of population-specific nomograms have significantly resulted in increased frequency of patients that achieve initial target vancomycin levels without any increase in toxicity (136). The development of vancomycin dosing nomograms that are exclusive for certain populations with similar covariate distributions potentially improves the attainment of PD targets. The exploratory analysis by Kullar et al. aiming to validate the effectiveness of a vancomycin nomogram for achieving target serum concentrations proved that excluding certain patient populations improves the precision and predictability of vancomycin PK targets (i.e.  $C_{\text{peak}}$ ,  $C_{\text{trough}}$ , AUC/MIC) (136-138).

## CHAPTER 3: METHODOLOGY

### 3.1 Introduction

This thesis is composed of three distinctive phases; each having its specific objectives. Consequently, three different study designs were applied as appropriate. Phase I was a multicenter retrospective observational study which aimed to assess the appropriateness of routine vancomycin TDM service in Qatar and to determine the clinical outcomes associated with the service. Phase II was a prospective RCT primarily aimed to compare the clinical and pharmacokinetic outcomes of the traditional peak-trough-based versus the new IDSA recommended trough-based vancomycin TDM approaches. Finally, Phase III comprised of a population pharmacokinetic analysis that was conducted to explore the local population's vancomycin pharmacokinetic parameters and the influence of population-specific covariates on vancomycin plasma exposure. The current chapter presents the methods of each phase separately.

### 3.2 Phase I: Multicenter retrospective evaluation of vancomycin TDM service appropriateness

#### *3.2.1 Study design*

Phase I was a multicenter retrospective electronic chart review of vancomycin TDM cases documented between January 2014 and October 2016. This period was chosen to reflect the “current status” of vancomycin TDM practices in the approved study sites. A summary of Phase I methods is presented in Figure 1.

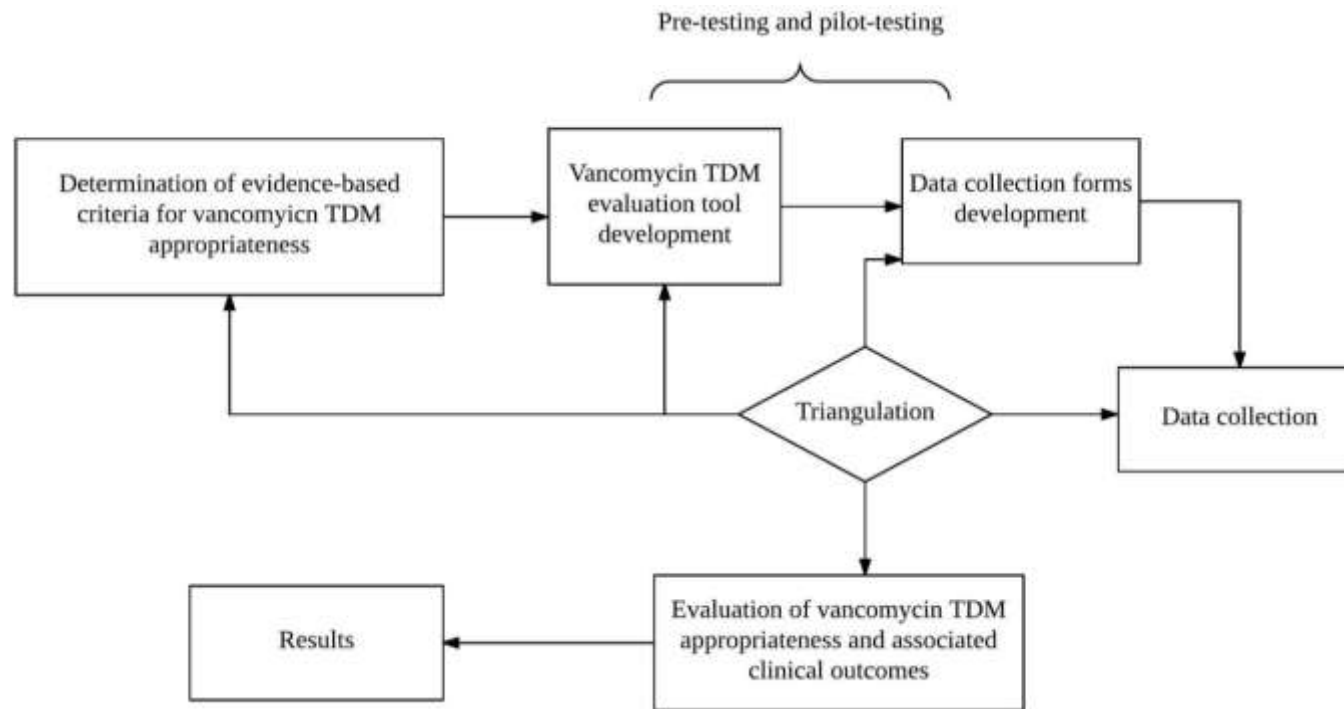


Figure 1: Methodology of multicenter routine vancomycin therapeutic drug monitoring service evaluation.

### *3.2.2 Study setting*

Hamad Medical Corporation (HMC) is the major provider of secondary and tertiary healthcare services to the population in Qatar. According to the 2015 annual report, HMC had a total of 302,853 admissions and 1,119,951 emergency visits and more than 3 million episodes of patient care ([139](#)). Our study included three hospitals, out of a total of eight hospitals under the umbrella of HMC. Hamad General Hospital (HGH) is a 603-bed tertiary hospital that encompasses most of medical services, such as emergency medicine, critical care, general medicine as well as specialized and sub-specialized clinical services. HGH is the largest provider of tertiary and highly specialized medical services, with a total of 142,930 patient admissions in 2015. Al-Khor Hospital (AKH) is a 110-bed hospital that serves the population in the northern region of Qatar, where 16,739 patient admissions and 207,794 emergency department visits were reported in 2015. Al-Wakrah Hospital (AWH) is a 210-bed hospital that serves approximately a population of 350,000 persons in southern Qatar. In 2015, 332,123 emergency visits and 58,714 patient admissions were reported in AWH. Both AKH and AWH provide critical care, general and emergency medicine, obstetrics and gynecology as well as trauma and surgery specialties care. In addition, AWH has a specialized burns unit.

### *3.2.3 Study population*

The study included three major hospitals under the umbrella of HMC in Qatar. Vancomycin TDM cases documented from January 2014 – October 2016 at AWH, AKH and HGH were reviewed.

### *3.2.4 Sample size and sampling technique*

Vancomycin TDM cases were selected using universal sampling approach (i.e. the entire patients/cases available included in the sample), due to the potentially small sample based on our preliminary inquiries. This implies that no sample size was determined and all cases of vancomycin TDM were included if they satisfied the pre-specified inclusion criteria.

### *3.2.5 Eligibility criteria*

A vancomycin TDM case was included if it was: 1) involving a non-dialysis adult patient aged 18 years or older; 2) documented between January 2014 and October 2016; 3) judged to have sufficient documentation on Cerner® to allow achieving the study objectives.

### *3.2.6 Data collection tools*

Data were collected through a pretested and pilot-tested data collection sheet using Microsoft Excel 2016. The data collection sheet was categorized into domains, with specific items under each domain. Table 1 summarizes the structure of the data collection form. Electronic medical records (EMR) from biochemistry laboratory as well as vancomycin inpatient pharmacy prescriptions (i.e. the data sources) were screened to identify any



vancomycin drug concentrations documented between January 2014 and October 2016. Comprehensive data collection was conducted and was structured to ensure capturing all information needed for accurate appropriateness assessment. Per patient file, only data documented during vancomycin treatment period were captured. Data from each vancomycin TDM case were collected by two independent data collectors who were pharmacists. This was to ensure accuracy and to avoid any misinterpretations of non-objective or ambiguous information from clinical notes.

Table 1

*Data collected from electronic medical records for the evaluation of vancomycin therapeutic drug monitoring practices*

Domain	Items
Patient demographics	Age, gender, weight, height, body mass index, ethnicity, allergies
Vancomycin blood specimen	Date collected, time collected, indication for ordering vancomycin TDM
Vancomycin dosing regimens	Route of administration, dose sequence, administration time and date, infusion duration, infusion starting time, infusion end time, dosing adjustments, number of dose adjustments, reason for dose adjustment, duration of vancomycin treatment
Laboratory and microbiology	All microbiology cultures were captured if documented between 14 days before and 14 days after the duration of vancomycin treatment, complete blood counts (CBCs), renal function tests, chemistry panel
Patient disease states	Indication for starting vancomycin, reason for discontinuing vancomycin, co-medications, comorbidities, history of present illness
Hospitalization	Hospital, ward, admission date, discharge date

### 3.2.7 Appropriateness assessment

Evidence-based *a priori* defined criteria were used for the evaluation of the vancomycin TDM service as shown in Table 2. Evidence-based clinical practice guidelines and applied clinical pharmacokinetic principles were used for the development of the assessment criteria (31, 32). Seven criteria were used to determine vancomycin TDM appropriateness in terms of pre-analytical and post-analytical practices. The developed tool was pre-tested and pilot tested. For practicality reasons and due to the pragmatic nature of the study, in all timing evaluations, a maximum of 15 minutes deviation from the appropriate blood collection timings was allowed. This was because the evaluated TDM cases occurred during the relatively new introduction of Cerner® in the included centers; it was observed that some nurses documented vancomycin dosing and blood specimen sampling collection earlier or later than the actual sampling time which reflects inaccurate documentation. For each appropriateness criterion, three outcomes were possible: 1) appropriate; 2) inappropriate and; 3) unable to determine due to insufficient documentation. A method of triangulation was applied; two pharmacists independently evaluated each vancomycin TDM case. The independent evaluations were then compared between the assessors. Any discrepancies were resolved through consensus.

Table 2

*Criteria used for the appropriateness assessment of vancomycin therapeutic drug monitoring service in Qatar*

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**Criterion-A: Appropriateness of indication**

This criterion was considered appropriate if vancomycin blood specimens (VBS) were drawn:

- to assure efficacy (i.e. if the therapeutic concentrations were achieved)
- to rule out toxicity
- to confirm therapeutic concentration post dose adjustments
- as a repeated sample collection due to suspected laboratory error
- as a repeated sample collection due to wrong blood sample collection time
- as a repeated sample collection to confirm an abnormal concentrations that is not physiologically plausible given the clinical status of the patient and other factors

**Criterion-B: Appropriateness of vancomycin blood specimen sampling time relative to the last dose (AST-LD)**

This criterion was considered appropriate if VBS was labelled as :

- “Vancomycin peak levels” (VPL): SDL was obtained 30-60 minutes post vancomycin infusion completion.
- “Vancomycin trough levels” (VTL): SDL was obtained within 30 minutes of the next dose. If the next dose was not administered to

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the patient per the prescription interval relative to the previous dose, the correct ‘next dose’ timing was calculated and considered in the appropriateness evaluation.

- “Vancomycin random level” (VRL): SDL was obtained at any point in time between the peak and trough concentrations in a dosing interval
- “Vancomycin level” (VL), consider AST-LD appropriate if it fulfilled any of the following:
  - i) *SDL was obtained within 30 minutes of the next dose; in this case, the specimen was considered a VTL that was mistakenly labeled and was highlighted as inappropriate labeling under criterion ‘C’*
  - ii) *SDL was obtained between 30-60 minutes post-infusion completion; in this case, the specimen was considered as a VPL that was mistakenly labelled and was highlighted as inappropriate labeling under criterion ‘C’*
  - iii) *SDL was obtained at any point in time between the peak and trough concentrations in a dosing interval; in this case, the specimen was considered VRL that was mistakenly labelled and was highlighted as inappropriate labeling under criterion ‘C’*

**Criterion-C: Appropriateness of vancomycin blood specimen labeling**

- Labeling of vancomycin blood specimen (VBS) was considered appropriate if it was labelled as:

- 
- i) VRL and AST-LD was appropriate
  - ii) VTL and AST-LD was appropriate
  - iii) VPL and AST-LD was appropriate

Labeling of VBS was considered inappropriate if it was labelled as VL regardless of the timing of blood collection

**Criterion-D: Appropriateness of vancomycin blood specimen sampling time relative to steady state attainment (AST-SS)**

This criterion was considered appropriate if:

- VBS was obtained at 3-5 half-lives of initiating vancomycin regimen
- VBS was taken 30 minutes after finishing the third dose of a consistent regimen onwards

**Criterion-E: Composite appropriateness of VBS sampling time (AST-C)**

AST-C was considered appropriate if both AST-SS and AST-LD were appropriate

**Criterion-F: Appropriateness of post-analytical action (PAA)**

PAA was considered appropriate if the provided clinical recommendation was based on correct interpretation by considering AST-C and patient clinical indices as per the following:

- If VBS had inappropriate AST-C, repeating VBS at correct AST-C was considered appropriate
  - For TDM cases comprising of non-therapeutic VTL only with correct AST-C
-

- 
- i) *It was assumed that dose-adjustments should follow the trough-only-based vancomycin TDM approach*
  - ii) *Doses rounded 100-250 mg were considered appropriate*
  - iii) *Dose intervals rounded to the nearest 6, 8, 12, 24 hours and multiples of 24 thereafter were considered appropriate*
  - iv) *If PAA was to change the dose and fix the interval, it was assumed that dose-only equation was used*
  - v) *If PAA was to change the interval while fixing the dose, it was assumed that interval-only equation was used*
  - vi) *PAA was considered inappropriate if dose and interval were changed simultaneously*
- For TDM cases compromising of non-therapeutic VTL and VPL, both with correct AST-C
    - i) *It was assumed that dose-adjustments should follow the peak- trough-based TDM approach*
    - ii) *Doses rounded 100-250 mg were considered appropriate*
    - iii) *Dose intervals rounded to the nearest 6, 8, 12, 24 hours and multiples of 24 thereafter were considered appropriate*
    - iv) *Dose adjustment calculations were repeated twice, using each of the highest and lowest boundaries of the therapeutic range at a time. Any dose-adjustments falling within the range was considered appropriate.*
    - v) *If vancomycin infusion time was not more than 120 minutes and the half-life was not less than 6 hours, IV bolus equations were*
-

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*used. Otherwise, IV intermittent infusion equations were applied*

- If the PAA was to discontinue vancomycin treatment in coincidence with non-therapeutic vancomycin concentration, the action was considered appropriate if
  - i) microbiological cultures confirmed that empirically started vancomycin treatment was no longer indicated*
  - ii) patient was experiencing vancomycin-related ADR (e.g. nephrotoxicity, Red Man syndrome, allergy, etc)*
  - iii) Patient was switched to an oral anti-MRSA agent in preparation for discharge*
- If vancomycin treatment was discontinued secondary to non-therapeutic vancomycin concentrations, but no other compelling reason, the PAA was considered inappropriate

**Criterion-G: Composite appropriateness of the provided vancomycin TDM service (CA-VTDMS)**

CA-VTDMS was considered appropriate if all the criteria (A-F) were appropriate

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### *3.2.8 Clinical outcomes assessment*

Clinical efficacy (including LOS) and safety outcomes were assessed using the definitions shown in Table 3.

### *3.2.9 Statistical analysis*

Descriptive and inferential statistics were performed using IBM Statistical Package for Social Sciences (SPSS) version 23. Chi-square test was used for categorical variables. Given that the data set was small ( $n < 2000$ ), Shapiro-Wilk test was used to determine the normality of continuous variables. Based on that, the non-parametric Mann-Whitney U test was used for continuous variables that were not normally distributed. A *priori* significance level of  $\leq 0.05$  (two-sided *p*-values) was considered statistically significant.

### *3.2.10 Ethical considerations*

This retrospective chart review was approved by Qatar University Institutional Review Board (QU-IRB) and the HMC Medical Research Center (HMC-MRC). Data collection was anonymous and patient identifiers were not collected.

Table 3

*Definitions of clinical outcome measures of Peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring randomized controlled trial*

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**A- Efficacy outcome measures ([19](#), [34](#), [42](#), [118](#))**

- |                     |  |
|---------------------|--|
| Therapeutic cure    | a. Clinical cure: Clinical signs/symptoms absent without the need for additional antibiotic treatment AND/OR               |
|                     | b. Microbiologic cure: Negative blood cultures indicating the eradication of the bacteria (MRSA)                           |
| Therapeutic failure | a. Clinical failure: Insufficient clinical response to initial therapy, necessitating antibiotic change                    |
|                     | b. Microbiological failure: Positive culture five or more days after initiation of an antibiotic                           |
|                     | c. Premature discontinuation of the study medication because of clinical/microbiological failure, or an adverse event (AE) |
|                     | d. All-cause mortality   |

**B- Safety outcome measures ([32](#), [140](#), [141](#))**

- |                |   |
|----------------|---|
| Neutropenia    | Absolute neutrophil counts less than 1000/ $\mu$ L ( <a href="#">140</a> , <a href="#">141</a> )  |
| Nephrotoxicity | “A minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or a $\geq$ 50% increase from baseline, whichever is greater) after several days of vancomycin therapy”(32) |
-

### 3.3 Phase II: Clinical and pharmacokinetic evaluation of peak-trough-based vs. trough-based vancomycin therapeutic drug monitoring: A randomized controlled trial

#### *3.3.1 Study design*

Phase II was a multicenter pragmatic parallel prospective RCT that was conducted from February 2016 to September 2016 in three tertiary care hospitals: HGH, AWH, and AKH. A summary of the methods used in Phase II is presented in Figure 2.

#### *3.3.2 Study setting*

Phase II was conducted at AWH, AKH, and HGH. The description of the 3 hospitals has been previously discussed in section 3.2.2.

#### *3.3.3 Study population and sampling*

The study population comprised of adult inpatients hospitalized at the designated hospitals who were started on vancomycin therapy and satisfied the eligibility criteria below. The required sample size was calculated *a priori* to be 150 patients, (75 patients per arm) ([142](#)). Attrition rate of 20%, significance level of 5%, and a power of 80% were considered in the power analysis. Based on the findings of previous two-group studies comparing different vancomycin dosing practices, 140-150 patients have resulted in detecting significant differences at a significance level of 0.05 and a power of 80% for pharmacokinetic endpoints ([117](#), [143](#)).

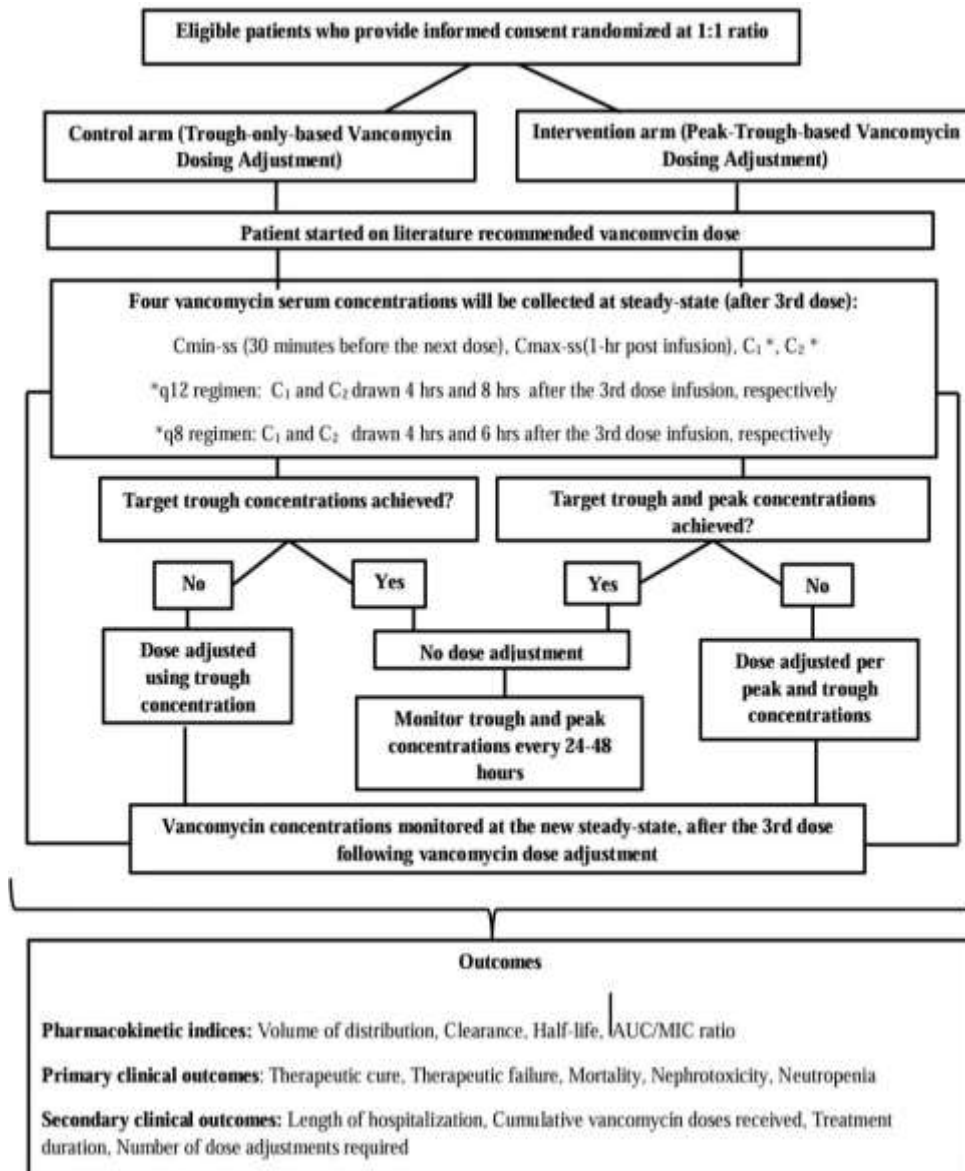


Figure 2: Methodology of the traditional peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring pragmatic randomized controlled trial.

#### *3.3.4 Eligibility criteria*

All vancomycin prescriptions in the pharmacy were screened twice daily to identify eligible subjects per the criteria detailed in Table 4. Only patients who provided consent were enrolled in the study.

Table 4

*Eligibility criteria for peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring randomized controlled trial*

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>• Adults 18 years or older</li> <li>• Suspected or confirmed Staphylococcal or other gram positive infection requiring treatment with vancomycin for at least 3 days based on attending physician's judgment</li> </ul>	<ul style="list-style-type: none"> <li>• Renal instability as defined by an abrupt absolute increase in SCr of <math>\geq 0.5</math> mg/dL from baseline or a percentage increase in SCr of <math>\geq 50\%</math> within 48h; Patient with end-stage renal disease on peritoneal dialysis or hemodialysis and transplant patients</li> <li>• Immunosuppressed patients: Active malignancy, receiving antineoplastic agents, HIV or have ANC <math>&lt; 1000</math> cells/mm<sup>3</sup></li> <li>• Vancomycin allergy or intolerance or History of recurrent resistant peritonitis</li> <li>• Administration of <math>&lt; 4</math> doses of vancomycin or for less than 72 h or Vancomycin for post-surgical infection prophylaxis</li> <li>• Pregnancy</li> <li>• Patients not able to undergo blood sampling per clinician judgment; Anuric patients: Urine output <math>&lt; 100</math>mL per day ; Symptomatic anemia; Hgb <math>&lt; 8</math> g/dL</li> </ul>

### *3.3.5 Informed consent procedures*

An informed consent form (ICF) in both Arabic and English was used [Appendix III]. Eligible patients were approached by the clinical pharmacist with whom they read and discussed the study details. After answering all questions, a participant was given freedom regarding the duration they need to inform the researchers/attending clinicians about their decision. If the patient did not understand Arabic or English, a third party translator (typically a nurse who can speak the patient's mother tongue) was asked for assistance. The participant, clinical pharmacist/attending clinician, and witnesses (when applicable) signed the consent form as a documented proof. If the patient was critically-ill, or unconscious, his/her legal guardian (i.e. a family member) was approached for the consent. If the family member/legal guardian provided consent, the patient would be enrolled in the trial. His/her data were only used if they consent after recovery from their critical health or mental status. If no recovery from the mental/health status occurred by the end of the trial, the family member/legal guardian consent was considered an approval to proceed with using the patient's data. Only if a patient was in coma and a family member/legal guardian could not be reached by any means, a waiver of consent was requested if the attending physician foresaw that the risk to the subject was low to no risk (in cases where blood samples were drawn from patients as part of routine care, and the same specimen could be used to measure vancomycin concentrations). Participants were free to withdraw their consent at any stage of the study. Data that were collected from withdrawing participants were used if it was sufficient to achieve at

least part of the study objectives, provided that the withdrawing participant agrees.

### *3.3.6 Randomization*

Participants who provided informed consent and fulfilled the eligibility criteria for the study (Table 4) were randomly assigned to one of the two study groups: (1) peak-trough group and; (2) trough-only group. An allocation ratio of 1:1 was applied using a computer-generated list of random numbers. This was crucial to eliminate selection bias and to ensure that both study arms are balanced in their baseline characteristics. Due to impracticality, this study was not blinded.

### *3.3.7 Study interventions*

All patients were initiated on vancomycin initial/empiric doses by the attending physician per recommendation in the literature/clinical practice guidelines prior to enrollment in the study ([32](#), [144-147](#)). Initiation or discontinuation of vancomycin treatment was the sole decision of the treating primary team and was not influenced by the RCT. This trial was of pragmatic in nature; thus, patients were treated as part of routine care. No co-medications, medical procedures, dietary restrictions or restrictions to participation in other concurrent research were applied for sole research purposes.

Eligible participants who provided informed consent were randomized to control arm (trough-only-based vancomycin dosing adjustment) or intervention arm (peak-trough-based vancomycin dosing



adjustment). In the two study arms, vancomycin target trough concentrations were as per recommended by HMC institutional guidelines and the clinical practice guidelines: more than 10 mg/L for less serious infections such as SSTIs; and up to 15 to 20 mg/L for complicated infections such as bacteremia, IE, osteomyelitis, meningitis, and hospital-acquired pneumonia (HAP) as well as serious SSTI (e.g. NF) caused by *S.aureus* (32). In the intervention arm, target vancomycin peak concentrations were 20–40 µg/L(31).

#### 3.3.7.1 Initial vancomycin blood samples collection

In both study arms, four initial vancomycin blood specimens were collected by venipuncture. Routine vancomycin trough concentrations were collected 30 minutes before the fourth dose according to HMC routine practice guidelines. For the study purpose, four vancomycin blood samples (10mL of blood for each) were obtained at 1-2 hrs post infusion ( $C_{max-ss}$ ), 30 minutes before the fourth dose ( $C_{min-ss}$ ) and two concentrations in between the peak and trough concentrations ( $C_1$ ,  $C_2$ ) after the fourth dose (i.e. at SS). If the patient was receiving a 12-hourly vancomycin regimen,  $C_1$  and  $C_2$  were drawn 4 hrs and 8 hrs post-infusion. On the other hand, if the patient was taking an 8-hourly regimen,  $C_1$  and  $C_2$  were drawn 4 hours and 6 hours post-infusion.

#### 3.3.7.2 Biospecimen analysis

Vancomycin blood specimens were collected and analyzed at HMC biochemistry laboratories using particle-enhanced turbidimetric inhibition

immunoassay (PETINA)([148](#)). Specimens from HGH and AKH were analyzed by Architect c16000, Abbott, USA ([149](#)). Specimens from AWH were analyzed by UniCel<sup>®</sup> DxC 600, Beckman Coulter, USA ([150](#)). To determine vancomycin susceptibilities, microbiology cultures were processed using broth microdilution test technique by BD Phoenix AP, USA ([151](#), [152](#)).

#### 3.3.7.3 Control arm: Trough-only-based vancomycin dosing adjustment

In the control arm, only trough vancomycin serum concentrations were considered in dosing adjustments. Peak vancomycin concentrations were not utilized in dosing adjustment calculations. Based on trough concentrations, if the patient did not achieve the serum concentration targets, a new dose or a new dosing interval was calculated using trough-only linear method equations [Appendix-I] ([77](#), [153](#)).

#### 3.3.7.4 Intervention arm: Peak-trough-based vancomycin dosing adjustment

Based on both peak and trough vancomycin concentrations, patient's individualized pharmacokinetic parameters were calculated. If any of the peak or trough concentrations were non-therapeutic, a new vancomycin dosing regimen was calculated and administered. IV bolus equations were used provided that the vancomycin infusion time was short relative to patient-specific vancomycin half-life. If this assumption was not valid due to augmented renal clearance or infusion durations more than one hour, IV intermittent infusion equations were used [Appendix-I] ([77](#), [153](#)).

### 3.3.7.5 Post-dosage adjustment monitoring

After any dosage adjustment, the time to new steady-state was calculated and post-dose adjustment peak and trough vancomycin concentrations were measured. If not therapeutic, dose adjustments were applied as discussed above. If vancomycin peak/trough concentrations were therapeutic and no dose adjustment was required, vancomycin troughs and peaks were monitored every 24-48 hours.

### 3.3.8 *Study endpoints*

#### 3.3.8.1 Primary outcome measures

Primary outcome measures of clinical effectiveness included: 1) vancomycin AUC/MIC ratio breakpoint for cure, 2) therapeutic cure (composite endpoint); 3) therapeutic failure (composite endpoint) and; 4) all-cause mortality. The primary safety measures were nephrotoxicity and neutropenia. Table 5 summarizes the definitions of the primary endpoints.

Table 5:

*Definitions of primary outcome measures for peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring randomized controlled trial*

Endpoints	Definition ( <a href="#">19</a> , <a href="#">34</a> , <a href="#">42</a> , <a href="#">118</a> )
Therapeutic cure	<ul style="list-style-type: none"> <li>a. Clinical cure: Clinical signs/symptoms absent without the need for additional antibiotic treatment AND/OR</li> <li>b. Microbiologic cure: Negative blood cultures indicating the eradication of bacteria</li> </ul>
Therapeutic failure	<ul style="list-style-type: none"> <li>a. Clinical failure: Insufficient clinical response to initial therapy necessitating antibiotic change</li> <li>b. Microbiological failure: Positive culture five or more days after initiation of an antibiotic</li> <li>c. Premature discontinuation of the study medication because of clinical/microbiological failure, or an adverse event (AE)</li> </ul>
Neutropenia	Absolute neutrophil counts less than 1000/ $\mu$ L ( <a href="#">140</a> , <a href="#">141</a> )
Nephrotoxicity	“A minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or at least 50% increase from baseline, whichever is greater) after several days of vancomycin therapy” ( <a href="#">32</a> )
All-cause mortality	Mortality from any cause during enrollment in the trial

### 3.3.8.2 Secondary outcome measures

Secondary outcomes included: 1) Length of hospital stay until therapeutic cure or failure; 2) Number of dose adjustments required until therapeutic cure or failure; 3) Cumulative vancomycin doses received until therapeutic cure or failure and; 4) Duration of vancomycin treatment until therapeutic cure or failure.

### 3.3.9 Statistical analysis

Descriptive and inferential statistics were conducted using SPSS v.23 (IBM®, Armonk; NY) to compare the differences in clinical outcomes between the traditional (i.e. peak-trough) and the new (i.e. trough only) vancomycin TDM practices. Standard descriptive statistics were used to describe the patients' demographic and baseline clinical characteristics. Summary of statistics such as means, standard deviations, range, frequencies and percentages were generated as appropriate. Homogeneity of the baseline data between the treatment arms was measured using appropriate tests including Student's *t*-test and Mann-Whitney *U*-test. For comparison between the groups or sub-groups, Student's *t*-test, Mann-Whitney *U*-test or Chi-square test was used as appropriate. Skewness test was applied to ensure the normality of data (choice of parametric vs. nonparametric tests). All comparisons were carried out using an *a priori* significance level of  $\leq 0.05$  (two-sided *p*-values). AUCs were calculated by NONMEM version 7.3 (ICON, USA), using the final population pharmacokinetic model resulting from Phase III. Classification and regression tree (CART) analysis was used

to assess the association between vancomycin cumulative doses, regimens, exposure (AUC) and clinical outcomes.

### *3.3.10 Ethical considerations*

This study was approved by HMC-MRC and QU-IRB as well as the research committees of AWH, AKH and HGH.

### 3.4 Phase III: Vancomycin population pharmacokinetics modeling

The population pharmacokinetic parameters of vancomycin have not been explored in Qatar or the MENA region. Yet, clinicians apply vancomycin dosing nomograms that have been established based on the covariate distributions and pharmacokinetic parameters of other populations. Phase III was conducted to explore the need for vancomycin dosing nomograms that are specific to Qatar's population, by establishing vancomycin pharmacokinetic parameters in the local population and comparing the findings to other populations.

#### *3.4.1 Study design*

Phase III employed non-linear mixed effects modeling (NLMEM) population pharmacokinetics (PPK) approach to determine the best model that describes vancomycin pharmacokinetics in the local population. Datasets from phase I (retrospective cohort) and phase II (prospective cohort) were merged and included in the PPK analysis. Figure 3 summarizes the procedures of phase III.

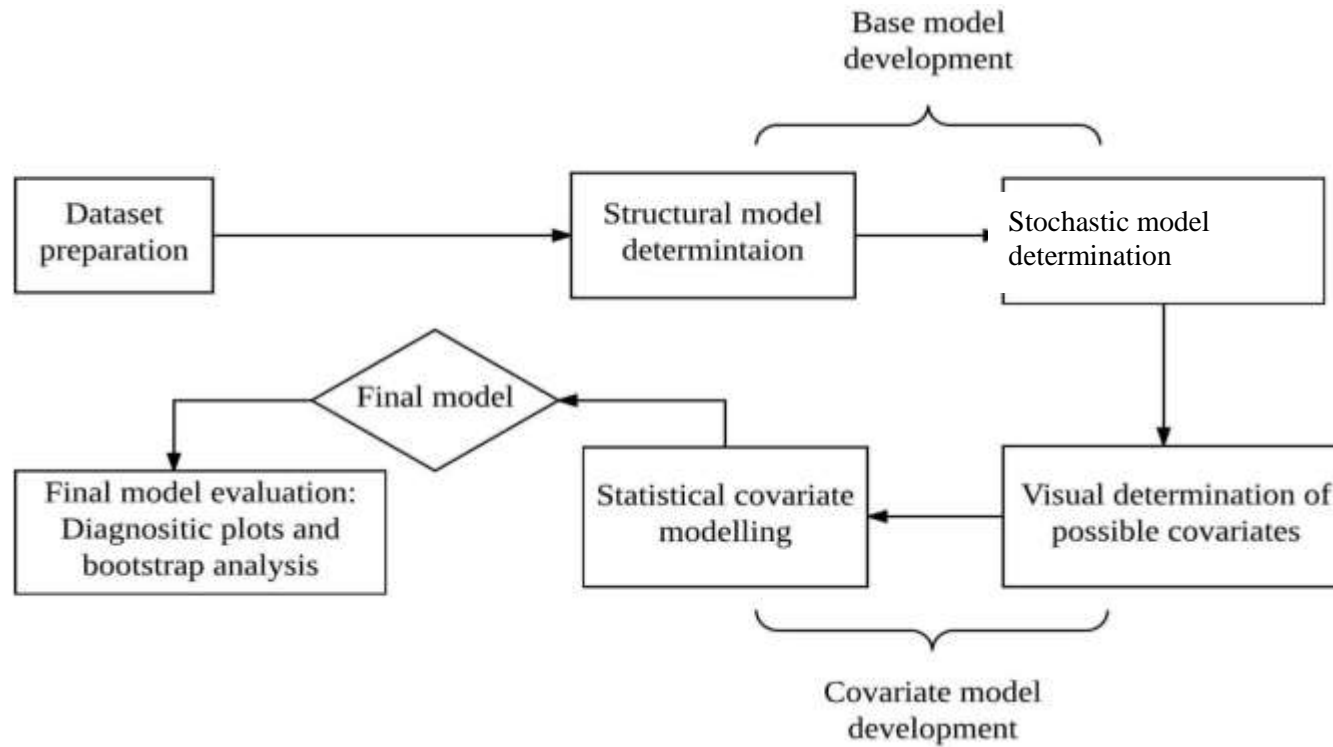


Figure 3: Methodology of vancomycin population pharmacokinetics modeling.



### *3.4.2 Study participants*

Phase III included all patients enrolled in phase I (retrospective cohort) and phase II (prospective cohort) of this project. All patients were hospitalized adults who were treated with intravenous vancomycin and were not receiving dialysis. From the retrospective cohort, all vancomycin blood concentration records were included if they corresponded to accurate dosing and sampling time documentation in the electronic medical records. From the prospective cohort, all vancomycin TDM records were included provided that the patient provided informed consent as discussed above in section (3.3.5).

### *3.4.3 Study setting*

Phase III included participants from the three major hospitals in Qatar that are located in different regions in the country and serve different patient populations. AWH and AKH are large secondary healthcare hospitals serving the southern and northern regions of Qatar, respectively. HGH is the largest secondary and tertiary healthcare hospital serving central Qatar. The retrospective cohort included vancomycin TDM data captured between January 2014 and October 2016 and that were documented after the introduction of Cerner® in these settings. The prospective cohort included vancomycin TDM cases enrolled between February 2016 and September 2016. Further details of the study setting have been previously discussed under sections (3.2.2).

#### *3.4.4 Vancomycin blood sampling*

In both cohorts, vancomycin blood specimens (10 mL) were obtained by venipuncture by the attending nurse. In the retrospective cohort, routine vancomycin TDM data were utilized and included peak, trough or random vancomycin blood specimens. In the prospective cohort, vancomycin blood specimens were obtained per a fixed schedule; routine vancomycin trough concentrations were collected 30 minutes before the fourth dose per HMC routine practice guidelines. For Phase II and Phase III study purposes, four vancomycin blood samples were obtained at 1-2 hrs post fourth dose infusion ( $C_{\max-ss}$ ), 30 minutes before the fifth dose ( $C_{\min-ss}$ ) and two concentrations in between the peak and trough concentrations ( $C_1$ ,  $C_2$ ) after the fourth dose (i.e. at SS). If the patient was receiving a 12-hourly vancomycin regimen,  $C_1$  and  $C_2$  were drawn 4 hours and 8 hours post-infusion. On the other hand, if the patient was taking an 8-hourly regimen,  $C_1$  and  $C_2$  were drawn 4 hours and 6 hours post-infusion.

#### *3.4.5 Vancomycin biospecimen analysis*

Vancomycin blood specimens were collected and analyzed at HMC biochemistry laboratories using particle-enhanced turbidimetric inhibition immunoassay (PETINA) ([148](#)). Specimens from HGH and AKH were analyzed by Architect c16000, Abbott, USA ([149](#)). Specimens from AWH were analyzed by UniCel<sup>®</sup> Dx<sub>C</sub> 600, Beckman Coulter, USA ([150](#)).

### *3.4.6 Dataset preparation*

Sections 3.2 and 3.3 above have discussed the data collection procedures of the retrospective and the prospective studies. Both datasets were merged and transformed into NONMEM specific data collection sheet using Microsoft Excel<sup>®</sup> 2016. Certain categorical variables were regrouped into dichotomous variables (e.g. nationality, co-medications, study group) to allow statistical detection of any differences (3.4.7.2). Within a dosing-monitoring time sequence, the first VBC below the limit of vancomycin assay quantification (BLQ) was recorded by limit of quantification (LOQ) divided by two. Within the same time series, any subsequent VBC <LOQ were recorded as missing.

### *3.4.7 Pharmacokinetic model development*

NLMEM approach was applied using NONMEM version 7.3 (ICON, USA) and PDx-Pop version 5.2 (ICON, USA). The estimation routine used was FOCE with INTERACTION (FOCE-I). Plots were generated using **R** version 3.3.2 (<https://www.r-project.org/>). A stepwise model building approach was applied and included: first, the development of the structural model followed by the development of the stochastic random effects model. Next, the covariates were modelled on the base model to determine significant vancomycin parameter-covariate relationships in our population. Lastly, the internal validation of the final model was applied.

### 3.4.7.1 Development of vancomycin base population pharmacokinetic model

#### 3.4.7.1.1 Determination of the structural model

As previous studies have reported vancomycin to follow one, two and three compartment linear models ([134](#), [154](#), [155](#)), these three structural models were compared. Built-in NONMEM Predictions for Population Pharmacokinetics (PREDPP) libraries were used. Specific PREDPP routines and trans subroutines were used to represent each structural model ([156](#)). The model with the least objective function value (OFV), highest precision in parameter estimates (least relative standard errors “%RSE”) as well as successful minimization and covariance steps was selected.

#### 3.4.7.1.2 Determination of the random effects stochastic model

Between-subject variability (BSV) was tested on each of the structural model parameters (CL, V<sub>c</sub>, V<sub>p</sub>, Q) separately and in simultaneous different combinations using an exponential model as expressed in Equation

1. BSV reflects the difference between the observed vancomycin parameter in the individual and the population parameter estimate.

$$\theta = \theta_{TV} * e^{\eta} \quad (\text{Eq. 1})$$

In this exponential model,  $\theta$  represents the individual parameter estimate,  $\theta_{TV}$  denotes the parameter typical value estimate of the population, and  $\eta$  represents the BSV with normal distribution, mean 0 and variance  $\omega^2$ .

The residual unexplained variability (RUV) was modelled by comparing three residual error models as shown in equations 2, 3, and 4.

$$Y = F + \varepsilon; \text{ Additive random error model (Eq.2)}$$

$$Y = F + (F * \varepsilon); \text{ proportional random error model (Eq.3)}$$

$$Y = F + (F * \epsilon_1) + \epsilon_2; \text{ combined error model (Eq.4)}$$

Y denotes the observed vancomycin concentration for  $i^{\text{th}}$  individual, F denotes the model predicted concentration in the  $i^{\text{th}}$  individual,  $\epsilon$  denotes residual unexplained error.

The variability in sampling techniques/instruments, biochemistry analytical procedures organizational clinical structure, as well as vancomycin TDM practices (i.e. accuracy in sampling time recording) may be a reason for unexplained residual variability. To determine the effect of study site, group, and visit number on the RUV, these categorical variables were modelled on the residual error model using Equation 5. Patients were grouped under two group classifications to test the effect of different study designs and sites on RUV. The retrospective dataset presented routine practice data that were recorded by nurses. Thus, retrospective data was more prone to inaccuracies in the documentation of sampling times versus the prospective dataset. The first classification was per study site (HGH vs. AWH. vs. AKH). The second classification was per the study design (prospective cohort vs. retrospective cohort). In case a patient had multiple visits under different study designs and study sites, the patient was classified under the site/group during which the longest duration of vancomycin treatment was received.

$$\text{If } x = n \rightarrow \text{RESI} = \theta_n \rightarrow Y = F + [F * (\epsilon * \text{RESI})]; \text{ (Eq.5)}$$

The tested independent variable (i.e. site, group, or visit number) is denoted by x, while n represents the category of the subject.

### 3.4.7.2 Determination of the covariate model

Covariates were modelled only on physiologic clinically relevant parameters that have clinical implications in patient dosing (Cl, Vc). Visual inspection of parameter-covariate plots was used for initial inspection and determination of potential covariates affecting clinically relevant PK parameters (Cl and Vc). Boxplots were used to examine categorical covariates, while scatter plots were used for continuous covariates.

Co-medications were included in NONMEM dataset if they were taken during vancomycin treatment and had probable PK interactions with vancomycin clearance that has been documented in the literature. The co-medications included in the NONMEM dataset included NSAIDs, amphotericin B, acyclovir, colistin, aminoglycosides, piperacillin/tazobactam. Due to the small number of patients taking the included co-medications, the co-medication category was regrouped into a dichotomous category that grouped all patients taking any of these co-medications into one group. Due to the diverse nationalities, a re-classification was applied. Subjects were grouped into four ethnicities: 1) Asian-Arab; 2) Non-Arab Asians; 3) African; 4) Others. CrCl was calculated using Cockcroft-Gault equation incorporating lean body weight (LBW) [Appendix-I]. Laboratory variables included liver enzymes (AST, ALT, ALP), albumin, WBC, Hgb.

Vancomycin pharmacokinetics may be effected by endogenous factors such as albumin and IgA levels and renal clearance ([157](#)). Studies have suggested that different disease states may impact the pharmacokinetics of antibiotics, by augmented renal clearance, changes in albumin levels or

other hemodynamic/physiological changes that result in changes in body composition or organ functions ([158-163](#)). Moreover, different disease states are associated with variabilities in mechanical/pharmacotherapeutic interventions, that may impact the disposition of antibiotics ([157](#), [158](#)). Since the evaluated cohort was heterogenous in terms of infection types, the diagnoses for which vancomycin treatment was initiated was grouped into four categories: 1) CNS infections; 2) LRT infections; 3) bacteremia; 4) localized SSTI. This classification was chosen to test the impact of variabilities in infected physiologic body compartment on vancomycin disposition.

All covariates were included for each vancomycin dose/serum concentration event. In case of missing covariates, structured method of imputation was applied. Last observation carried backward (LOCB) was applied if the covariate was missing at baseline; 2) last observation carried forward (LOCF) was applied if the covariate was missing at the last vancomycin dosing/concentration events with no successive covariate data within the time series. If the covariate was missing at a time-point falling in between two available successive and precedent covariate values, interpolation method was applied [Appendix-I]. The final NONMEM dataset included 2937 records that corresponded to 156 patients. Table 6 summarizes the total imputed records included in the final NONMEM dataset. Based on visual inspection and physiological plausibility, covariates revealing potential relationships with  $V_c$ , or  $Cl$  were carried on to ‘Forward-selection-backward-elimination steps’.

Table 6

*Imputations included in the final NONMEM dataset*

Imputation type	Number of records imputed		Number of subjects imputed	
	n (%)		n (%)	
	SCr (n=722)	LBW (n=25)	SCr (n=69)	LBW (n=4)
LOCB	88 (12.2)	10 (40)	17 (24.7)	1 (25)
Interpolation	497 (68.8)	10 (40)	40 (58)	2 (50)
LOCF	137 (19)	5 (20)	26 (37.7)	1 (25)

LOCF: last observation carried forward; LOCB: last observation carried backward



### 3.4.7.2.1 Forward covariate selection procedure

During forward-selection, covariate-CL and covariate-Vc models were tested separately. For each continuous covariate-parameter relationship, different mathematical models were tested as expressed in equations 6 - 9. The mathematical models incorporated population parameters. Per parameter-covariate relationship, the mathematical model resulting in least OFV was considered for forward selection steps. Dichotomous covariates were modelled using equation 10, using gender as an example, where  $\theta_m$ , and  $\theta_f$  denote vancomycin PK parameter in males and females, respectively.

$$\theta_{TV} = \theta_{\text{median}} * [\text{COV}_i / \text{COV}_{\text{median}}] * \theta_j \quad \text{Eq.6}$$

$$\theta_{TV} = \theta_{\text{median}} * [\text{COV}_i / \text{COV}_{\text{median}}]** \theta_j \quad \text{Eq.7}$$

$$\theta_{TV} = \theta_{\text{median}} + [\text{COV}_i / \text{COV}_{\text{median}}]** \theta_j \quad \text{Eq.8}$$

$$\theta_{TV} = \theta_{\text{median}} + [\text{COV}_i / \text{COV}_{\text{median}}] * \theta_j \quad \text{Eq.9}$$

$$\theta_{TV} = \theta_m * \theta_f^{\text{GENDER}} \quad \text{Eq. 10}$$

In an individual  $i$ ,  $\theta_{TV}$  and  $\text{COV}_i$  represents the typical vancomycin PK parameter and continuous covariate value, respectively. Population median continuous covariate values were expressed as  $\text{COV}_{\text{median}}$ , whereas the population median vancomycin PK parameter estimate was represented by  $\theta_{\text{median}}$ . To express the relationship between the vancomycin PK parameter in an individual with median covariate value, the scaling factor  $\theta_j$  was incorporated.

Separate runs were generated per covariate-parameter model. The OFV of these separate runs was compared to the OFV of the base model. Covariates resulting in overall OFV decrease of at least 3.84 were considered significant at  $\alpha=0.05$ . Covariate-parameter models resulting in significant

decreases in the OFV were ranked in descending order, per the drop in OFV compared to the base model. The covariate resulting in the most significant drop in the OFV was kept in the model and the other significant covariates were added once at a time to the most significant covariate model during separate model runs. If the addition of less significant covariate on top of the most significant covariate resulted OFV change  $<3.84$ , the less significant covariate was excluded. The covariates kept after completing the forward-selection procedures were next included in the backward-elimination steps.

#### 3.4.7.2.2 Backward covariate elimination procedure

During backward elimination, each covariate was excluded from the model once at a time in separate iterations. If the exclusion of the covariate from the model resulted in OFV increase of at least 6.6 units, the covariate was considered statistically significant at  $\alpha=0.01$ . Thus, it was kept in the model. Otherwise, the covariate was excluded from the final model. . RSE% was used to determine the precision of vancomycin population PK parameter estimates at different iterations. Also, the success of both model minimization and covariance steps during NONMEM runs was considered in the evaluation of different iterations.

#### 3.4.7.3 Final model evaluation

During the various model building steps, the appropriateness of the model was evaluated using goodness-of-fit (GOF) plots, eta plots, and residual error plots. GOF plots included comparing the individual-observed versus model-predicted population and individual vancomycin serum concentrations. To examine the possibility of the presence of underlying

subpopulations, eta plots were generated. Residual error plots were examined to assure that the model was not biased.

Finally, the internal validation of the final model was checked by bootstrap analysis using sampling with replacement. To determine the extent of uncertainty of the final model estimates, nonparametric bootstrap sampling with replacement was conducted. Non-parametric bootstrap sampling with replacement overlooks the final model estimates, and approximates the population by generating random samples (i.e. iterations) with replacement of the observed data, while maintaining the sample size of the original dataset (164). This allows the detection of any systematic bias and the assessment of the stability of the final model estimates. Five-hundred data replicates were run. The number of successful runs was examined. The agreement between the final parameter estimates, the respective confidence intervals, and standard errors of the developed final model (observed vancomycin concentrations) and the bootstrap results (simulated vancomycin concentrations) were compared.

#### *3.4.8 Comparison between Qatar's population vancomycin clinical pharmacokinetic parameters and other populations*

To assess the need for population-specific vancomycin dosing nomograms, the local population's vancomycin clinical pharmacokinetic parameters generated from the modeling were compared to the findings in other populations. The scientific literature was screened for studies that explored vancomycin disposition in adult patients who were not on dialysis. Vancomycin clinical pharmacokinetic parameters from studies that reported

two-compartment models through the incorporation of NLMEM were summarized and compared to the findings from the local population studied in this project.

## CHAPTER 4: RESULTS

### 4.1 Phase 1: Multicenter retrospective evaluation of vancomycin therapeutic drug monitoring service appropriateness

#### *4.1.1 Demographic and clinical characteristics of vancomycin therapeutic drug monitoring cases*

A total of 208 vancomycin TDM cases that were performed among 99 adult non-dialysis patients between 2014 and 2016 were evaluated. A median (IQR) of 2 (3) vancomycin TDM were conducted per patient. The cases were obtained from the three study hospitals with the majority (90.8%, n=189) of the patient cases being from Asia. The most frequent vancomycin-treated infections among the cases were sepsis/septic shock (16.8%, n=35), SSTI (15.4%, n=32), and LRTI (14.9%, n=31). Most of the patient cases were obtained from the medical wards (51.4%, n=107), followed by intensive care units (33.7%, n=70), surgical wards (12.5%, n=26), and burn units (2.4%, n=5). Clinicians ordered vancomycin trough concentrations (VTC) in 74.5% (n=155) of the cases, while the type of ordered vancomycin concentration was unspecified in 23.6% (n=49) of the cases. Indications for ordering vancomycin TDM were to ensure efficacy (70.7%, n=147), confirm safety (12.5%, n=26), or were unknown (16.8%, n=35).

The median (IQR) subtherapeutic vancomycin concentration was 9 (7.95) mg/L, with 6.3% (n=13) of all vancomycin concentrations below the quantification limit of vancomycin assay (BLQ). According to clinicians' interpretation of vancomycin blood concentrations, most (51%, n=106) were subtherapeutic, while the minority were within the therapeutic window

(13.5%, n=28) or supratherapeutic (13%, n=27). However, interpretation was not possible in 22.6% (n=47) of the cases that had incomplete vancomycin dosing records or corresponded to vancomycin blood specimens that were judged to be collected during distribution phase or vancomycin ongoing infusion. Table 7 summarizes the characteristics of the evaluated vancomycin TDM cases.

Table 7

*Characteristics of evaluated routine vancomycin therapeutic drug monitoring cases (N=208)*

---

Age in years, , [median(IQR)]	[43 (25)]
Weight (kg)* , [median(IQR)]	[70.5 (28.5)]
Height (cm)* , [median(IQR)]	[167 (17)]
<b>Ethnicity, n (%)</b>	
<i>Asian (Arab)</i>	100 (48.1)
<i>Asian (non-Arab)</i>	89 (42.8)
<i>African</i>	12 (5.8)
<i>Other</i> <sup>€*</sup>	7 (3.4)
<b>Nationality, n (%)</b>	
<i>Qatar</i>	60 (28.8)
<i>India</i>	30 (14.4)
<i>Palestinian</i> <sup>€</sup>	17 (8.2)
<i>Bangladesh</i>	17 (8.2)
<i>Egypt</i>	15 (7.2)
<i>Pakistan</i>	14 ( 6.7)
<i>Others</i> <sup>€€</sup>	55 (26.5)
<b>Hospital n (%)</b>	
<i>Al-Khor Hospital</i>	95 (45.7)
<i>Al-Wakrah Hospital</i>	55 (26.4)
<i>Hamad General Hospital</i>	58 (27.9)

---

Table 7

*Characteristics of evaluated routine vancomycin therapeutic drug monitoring cases (N=208) (continued)*

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<b>Ward of hospitalization , n (%)</b>	
<i>Medical ward</i>	107 (51.4)
<i>Critical care units</i> <sup>Δ</sup>	70 (33.7)
<i>Surgical ward</i>	26 (12.5)
<i>Burns unit</i>	5 (2.4)
<b>Infection type*, n (%)</b>	
<i>Sepsis and septic shock</i>	35 (16.8)
<i>Skin and soft tissue infections</i>	32 (15.4)
<i>Lower respiratory tract infections</i>	31 (14.9)
<i>Bone and joint infections</i>	27 (13)
<i>Meningitis</i>	26 (12.5)
<i>Bacteremia</i>	17 (8.2)
<i>Intra-abdominal infections</i>	14 (6.7)
<i>Urinary tract infections</i>	10 (4.8)
<i>Infective endocarditis</i>	10 (4.8)

---



Table 7

*Characteristics of evaluated routine vancomycin therapeutic drug monitoring cases (N=208) (continued)*

---

<b>Vancomycin dosing details</b>	
<i>Initial vancomycin dosing regimen</i>	[1000 (0)]
<i>(mg), [median (IQR)]</i>	
<i>Total vancomycin doses received</i>	
<i>before vancomycin blood specimen</i>	[4 (3)]
<i>collection, [median (IQR)]</i>	
<i>Total vancomycin doses received,</i>	[11 (21)]
<i>[median (IQR)]</i>	
<i>Vancomycin TDM cases per patient</i>	[2 (3)]
<b>Vancomycin route of administration*, n (%)</b>	
<i>Intravenous</i>	197 (99.5)
<i>Nasogastric</i>	1 (0.5)
<b>Vancomycin dosing frequency (hrs), n (%)</b>	
<i>single stat dose</i>	15 (7.2)
<i>q 6</i>	6 (2.9)
<i>q 8</i>	54 (26)
<i>q 12</i>	114 (54.7)
<i>q 24</i>	18 (8.7)
<i>q 48</i>	1 (0.5)

---

Table 7

*Characteristics of evaluated routine vancomycin therapeutic drug monitoring cases (N=208) (continued)*

---

<b>Vancomycin infusion duration*, n (%)</b>	
<i>1-hour</i>	171 (87.2)
<i>1.5-hour</i>	5 (2.6)
<i>2-hour</i>	18 (9.2)
<i>4-hour</i>	2 (1)
<b>Type of ordered vancomycin blood concentration <sup>a</sup>, n (%)</b>	
<i>Trough</i>	155 (74.5)
<i>Peak</i>	2 (1)
<i>Random</i>	2 (1)
<i>Unclassified <sup>aa</sup></i>	49 (23.6)
<b>Indication for ordering vancomycin TDM, n (%)</b>	
<i>Confirm efficacy</i>	147 (70.7)
<i>Confirm safety</i>	26 (12.5)
<i>Unknown</i>	35 (16.8)
<b>Vancomycin blood concentration <sup>b</sup> (mg/L), [median (IQR)]</b>	
<i>Trough</i>	[9 (7.95)]
<i>Peak</i>	-
<i>Random</i>	[ 11 (10.95)]
<i>Unspecified <sup>bb</sup></i>	[6.2 (12.4)]

---

Table 7

*Characteristics of evaluated routine vancomycin therapeutic drug monitoring cases (N=208) (continued)*

---

**Vancomycin blood concentration pertinent to assay detection**

**limit, n (%)**

<i>Below assay detection limit</i>	13 (6.3)
<i>Within assay detection limit</i>	195 (93.7)

**Clinician interpretation of vancomycin blood concentration**

**<sup>a</sup>, n (%)**

<i>Therapeutic</i>	28 (13.5)
<i>Subtherapeutic</i>	106 (51)
<i>Supratherapeutic</i>	27 (13)
<i>Unspecified<sup>aa,bb</sup></i>	47 (22.5)

---

\*missing values; €includes Syria and Jordan; €\*includes Britain and USA; €€includes Ghana, Philippines, Yemen, Sudan, Tanzania; <sup>Δ</sup> includes medical, surgical and trauma intensive care units; <sup>a</sup>per the label of ordered vancomycin blood concentration (VBC) disregarding the actual sampling time; <sup>aa</sup>documented as “vancomycin level”; <sup>b</sup>type of VBC determined per the actual sampling time; <sup>bb</sup>includes: 1) VBC collected during vancomycin infusion or distribution phase or unclassified VBC due to insufficient documentation of vancomycin dosing data

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#### *4.1.2 Clinical effectiveness and safety outcomes related to vancomycin TDM cases*

Vancomycin TDM cases were associated with suboptimal clinical outcomes, prolonged hospitalization and adverse events [Table 8]. Fifty percent of the TDM cases were associated with therapeutic failures (n=104), corresponding to 56.6% (n=56) of all patients. Out of 89 evaluable patients, nephrotoxicity occurred in 13 patients, corresponding to 13.3% (n=26) of vancomycin TDM cases [Table 8]. Out of 92 evaluable patients, neutropenia occurred in 6 patients, corresponding to 6.5% of vancomycin TDM cases [Table 8]. All-cause mortality rate was 9.1%. Nine patients died, corresponding to 12% of all vancomycin TDM cases. Table 8 summarizes the clinical outcomes associated with vancomycin TDM cases.

Table 8

*Clinical outcomes associated with routine vancomycin therapeutic drug monitoring cases (N=208)*

---

**Clinical effectiveness outcomes of vancomycin TDM cases**

Therapeutic cure, n (%)	104 (50)
Therapeutic failure, n (%)	104 (50)
Vancomycin treatment duration (days), [median (IQR)]	[8 (2)]
Length of hospitalization (days), [median (IQR)]	[25 (50)]

**Clinical safety outcomes of vancomycin TDM cases**

Nephrotoxicity <sup>§</sup> , n (%)	26 (13.3)
Neutropenia <sup>§§</sup> , n (%)	13 (6.5)
All-cause mortality, n (%)	25 (12)

---

<sup>§</sup> missing values for 13 vancomycin TDM cases performed in 10 patients

<sup>§§</sup> missing values for 9 vancomycin TDM cases performed in 7 patients

---

#### *4.1.3 Composite appropriateness of vancomycin therapeutic drug monitoring practices*

The composite appropriateness of vancomycin TDM service was achieved in only 9.6% (n=20) of all evaluated cases, with the vast majority conducted inappropriately (90.4%, n=188) [Table 9]. The majority (83.8%, n=83) of the patients did not receive a compositely appropriate vancomycin TDM service, whereas a minority (16.2%, n=16) received at least one compositely appropriate vancomycin TDM service. Only eight patients (8.08%) did not receive any compositely inappropriate vancomycin TDM service. Table 9 summarizes the appropriateness of vancomycin TDM practices.

##### *4.1.3.1 Appropriateness of pre-analytical vancomycin therapeutic drug monitoring practices*

Most of the vancomycin TDM cases were appropriately indicated (77.4%, n=161) and blood specimens were sampled at steady-state (81.3%, n=169). The inappropriately indicated vancomycin TDM cases (22.6%, n=47) included one case of nasogastrically administered vancomycin treatment [Table 7]. Vancomycin TDM practices did not achieve appropriate sampling times (AST-C) at most times (70.7%, n=147), due to inappropriate sampling relative to the last administered vancomycin dose (69.7%, n=145) as well as sampling relative to attaining steady-state (18.8%, n=39). TDM documentation practices and VBC labeling were suboptimal in 44.7% (n=93)

and 81.7% (n=170) of the cases, respectively. Table 9 summarizes the appropriateness of vancomycin TDM practices.

Poor alignment was found while examining the EMR documented VBC labeling and the actual sampling time recorded by the personnel collecting the respective vancomycin blood specimens [Table 10]. According to the actual sampling times documented in the EMR, more than half of the ordered troughs were incorrectly labeled and corresponded to clinically irrelevant random vancomycin blood levels (65.2%, n=101) or distribution phase samples (9%, n=14) [Table-10]. Overall, the actual sampling times revealed that most vancomycin blood specimens (61.5%, n=128) corresponded to vancomycin random concentrations. Discordant to HMC guidelines that follow IDSA-ASHP-2009 vancomycin trough-only monitoring recommendations, actual sampling times rarely (21.6%, n=45) corresponded to vancomycin trough concentrations. Table 10 summarizes the discrepancy between actual vancomycin specimen sampling times and documented labeling of vancomycin blood specimens.

Table 9

*Evaluation of the appropriateness of vancomycin therapeutic drug monitoring service*

Appropriateness Index (N = 208) [n (%)]	Composite appropriateness of vancomycin TDM cases (CA-VTDM)		
	Inappropriate (N=188)	Appropriate (N=20) n (%)	p-value*
<b>Indication appropriateness of vancomycin TDM service</b>			
Inappropriate [47 (22.6) ]	47 (25)	0 (0)	0.011
Appropriate ]161 (77.4)]	141 (75)	20 (100)	
<b>Sampling time appropriateness relative to the last dose (AST-LD)</b>			
Inappropriate [145 (69.7)[	145 (77.1)	0 (0)	< 0.001
Appropriate ]63 (30.3)[	43 (22.9)	20 (100)	
<b>Vancomycin blood concentration labeling appropriateness</b>			
Inappropriate ]170 (81.7)[	170 (90.4)	0 (0)	< 0.001
Appropriate ]38 (18.3)[	18 (9.6%)	20 (100)	
<b>Sampling time appropriateness relative to steady-state attainment (AST-SS)</b>			
Inappropriate ]39 (18.8)[	39 (20.7)	0 (0)	0.024
Appropriate ]169 (81.3)[	149 (79.3)	20 (100)	
<b>Composite sampling time appropriateness (AST-C)<sup>§</sup></b>			
Inappropriate [147 (70.7)[	147 (78.2)	0 (0)	< 0.001
Appropriate [61 (29.3)[	41 (21.8)	20 (100)	



Table 9

*Evaluation of the appropriateness of vancomycin therapeutic drug monitoring service (continued)*

Appropriateness index (N=208) [n (%)]	Composite appropriateness of vancomycin TDM cases		
	Inappropriate (N=188)	Appropriate (N=20)	p-value*
			n (%)
<b>Post-analytical action appropriateness</b>			
Inappropriate [137 (65.9)]	137 (72.9)	0 (0)	< 0.001
Appropriate [71 (34.1)]	51 (27.1)	20 (100)	
<b>Documentation appropriateness related to vancomycin treatment indication</b>			
Inappropriate [9 (4.3)]	9 (4.8)	0 (0)	0.317
Appropriate [199 (95.4)]	179 (95.2)	20 (100)	
<b>Documentation appropriateness related to vancomycin TDM service indication</b>			
Inappropriate [39 (18.8)]	39 (20.7)	0 (0)	0.024
Appropriate [169 (81.3)]	149 (79.3)	20 (100)	
<b>Documentation appropriateness of vancomycin blood concentration labeling</b>			
Inappropriate [21(10.1)]	21 (11.2)	0 (0)	0.115
Appropriate [187 (89.9)]	167 (88.8)	20 (100)	
<b>Documentation appropriateness related to vancomycin sampling time</b>			
Inappropriate [22 (10.6)]	22 (11.7)	0 (0)	0.106
Appropriate [186 (89.4)]	166 (88.3)	20 (100)	

Table 9

*Evaluation of the appropriateness of vancomycin therapeutic drug monitoring service (continued)*

---

<b>Documentation appropriateness related to vancomycin blood concentration interpretation</b>			
Inappropriate [46 (22.1)[	46 (24.5)	0 (0)	0.048
Appropriate [162 (77.9 )]	142 (75.5)	20 (100)	
<b>Documentation appropriateness related to post-analytical action</b>			
Inappropriate [20 (9.6)[	168 (89.4)	0 (0)	0.125
Appropriate ]188 (90.4 )]	20 (10.6)	20 (100)	
<b>Composite documentation appropriateness<sup>§§</sup></b>			
Inappropriate [93 (44.7)[	91 (48.4)	0 (0)	< 0.001
Appropriate ]115 (55.3)[	97 (51.6)	20 (100)	

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\*Chi-square test was applied in calculating p-values; <sup>§</sup>includes both AST-SS and AST-LD; <sup>§§</sup>includes all documentation appropriateness indices

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Table 10

*Labeling appropriateness of vancomycin blood concentrations*

Applied labeling <sup>§§</sup> (N=208)	Appropriate labeling <sup>ε</sup>				p-value*
	VTC (n=45)	VRC (n=128)	Vancomycin pre-distribution concentration <sup>a</sup> (n=21)	Undetermined <sup>b</sup> (n=14)	
[n (%)]	n (%)				
“ Vancomycin trough level”[155 (74.5)]	36 (23.2)	101 (65.2)	14 (9)	4 (2.6)	
Vancomycin peak level”[2 (1)]	1(50)	0 (0)	1 (50)	0 (0)	0.314
“ Vancomycin random level”[2(1)]	0 (0)	2 (100)	0 (0)	0 (0)	
“ Vancomycin level” [49(23.6)]	8 (16.3)	25 (51.1)	6 (12.2)	10 (20.4)	

\*Chi-square test was applied; <sup>§§</sup> quoted as documented in patient medical records; <sup>ε</sup> based on the last administered vancomycin dose; VTC: vancomycin trough concentration; VRC: vancomycin random concentrations; <sup>a</sup> includes vancomycin blood specimens collected during vancomycin infusion or pre-distribution phase ; <sup>b</sup> missing values due to insufficient documentation of vancomycin dosing data; <sup>c</sup> unclassified

#### 4.1.3.2 Appropriateness of post-analytical vancomycin TDM service practices

Post-analytical actions (PAAs) were assessed for 90.4% (n=188) of TDM cases [Table 9], due to ambiguous or missing documentation of post-analytical actions in 9.6% (n=20) of the cases [Table-11]. Statistically significant differences were revealed when appropriate versus applied post-analytical actions were compared [Table 11; p-value<0.001]. From all assessed PAAs, re-ordering vancomycin blood specimen was the most frequent (64.4%, n=121) appropriate PAA that should have been conducted, secondary to the high rates of inappropriate vancomycin trough concentration sampling times. Yet, re-ordering vancomycin blood specimen was applied minimally (9.9%, n=12) of all indicated cases. Inappropriate sampling times resulted in false vancomycin blood concentrations, accounting for the implementation of inappropriate vancomycin discontinuation in (9.1%, n=11) or unindicated dose adjustments (42.1%, n=51) when re-ordering vancomycin TDM was the appropriate PAA. Table 11 summarizes the appropriateness of PAA of the vancomycin TDM cases.

Table 11

*Appropriateness of post-analytical actions of vancomycin therapeutic drug monitoring service*

Applied post-analytical action <sup>§</sup> (N=188)	Appropriate post-analytical action (N=188) <sup>§</sup>				p-value*
	Adjust dose (N=34)	Continue current dose (N=14)	Re-order vancomycin TDM <sup>§§</sup> (N=121)	Hold/discontinue vancomycin treatment (N=19)	
[n (%)]	n (%)				
Adjust dose [69 (36.7)]	18 (26.1)	0 (0)	51 (73.9)	0 (0)	
Continue current dose [73 (38)]	11 (15)	14 (19.2)	47 (64.4)	1 (1.4)	
Re-order vancomycin TDM <sup>§§</sup> [12 (6.4)]	0 (0)	0 (0)	12 (100)	0 (0)	<0.001
Hold/discontinue vancomycin treatment [34 (18.1)]	5 (14.6)	0 (0)	11 (32.4)	18 (53)	

<sup>§</sup> missing post-analytical action data for 20 vancomycin TDM cases; <sup>§§</sup> due to inappropriate sampling time or suspected laboratory error; \* Chi-square and Fisher's exact tests were applied as appropriate

The present evaluation revealed poor dose-adjustment practices pertaining to vancomycin TDM [Table 12]. Of 69 applied dose adjustments, the majority (73.9%, n=51) were not indicated. Conversely, dose adjustment was not applied when indicated in 16 vancomycin TDM cases. TDM-directed calculations that were implemented for the computation of new vancomycin dosing regimens were at most times (63.4%, n=44) questionable. The majority of these dose adjustment computations (60.2%, n=42) resulted in clinically significant subtherapeutic new dose recommendations. According to those calculations, patients were under-dosed [median (IQR): single dose deviation -750 (581) mg; total daily dose deviation: -1500 (1000) mg]. Table 12 summarizes the appropriateness of dose adjustment practices.

Table 12

*Appropriateness of the applied vancomycin dose adjustments (N=69)*


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<b>No dose adjustment applied when indicated, n (%)</b>	16 (47.1)
<b>Applied dosing adjustments</b>	
Dose adjustment applied when indicated	18 (26.1)
Dose adjustment applied when not indicated	51 (73.9)
<b>Dose-adjustment method applied, n (%)</b>	
Trough-only-based: dose change	54 (78.3)
Trough-only-based: interval change	9 (13)
Trough-only-based: Undetermined <sup>§§</sup>	6 (8.7)
<b>Calculation of the applied dosing adjustments, n (%)</b>	
Appropriate: Patient received a correctly calculated new dose	25 (36.6)
Inappropriate: Patient was under-dosed	42 (60.2)
Inappropriate: Patient was over-dosed	2 (3.2)
<b>Single dose deviation (mg), [median (IQR)]</b>	
Appropriate calculation: Patient received a correct new dose	[0 (0)]
Inappropriate calculation: Patient was under-dosed	[750 (581)]
Inappropriate calculation: Patient was over-dosed	[61 (0)]

---

Table 12

*Appropriateness of the applied vancomycin dose adjustments (N=69; continued)*

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**Total daily dose vancomycin dose deviation (mg), [median (IQR)]**

Appropriate calculation: Patient received a correct new dose [0 (0)]

Inappropriate calculation: Patient was under-dosed [1500 (1000)]

Inappropriate calculation: Patient was over-dosed [145 (0)]

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<sup>§</sup> Assessed while assuming the appropriateness of all other appropriateness

indices; <sup>§§</sup> Simultaneous adjustment of vancomycin dose and dosing interval were applied

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#### *4.1.4 Association between vancomycin TDM appropriateness indices and clinical outcomes*

##### 4.1.4.1 Association between vancomycin TDM appropriateness and effectiveness outcomes

Appropriate vancomycin TDM practices were significantly associated with higher rates of clinical effectiveness [Table 13]. Overall, appropriate vancomycin TDM practices compared to inappropriate vancomycin TDM practices were associated with significantly higher rates of therapeutic cures [75% vs. 47.3%; p-value=0.009; Figure 4]. A similar trend was observed for several individual vancomycin TDM appropriateness indices; appropriate VBC labeling, sampling time at steady-state, post-analytical actions and documentation practices were significantly associated with higher rates of clinical cures and lower rates of clinical failures (p-value<0.05). Furthermore, inappropriate indications, inappropriate composite sampling time, and inappropriate sampling time relative to the last administered vancomycin dose were all associated with insignificantly higher rates of clinical failures (p-value>0.05). Table 13 summarizes the association between clinical effectiveness and vancomycin TDM service appropriateness indices.

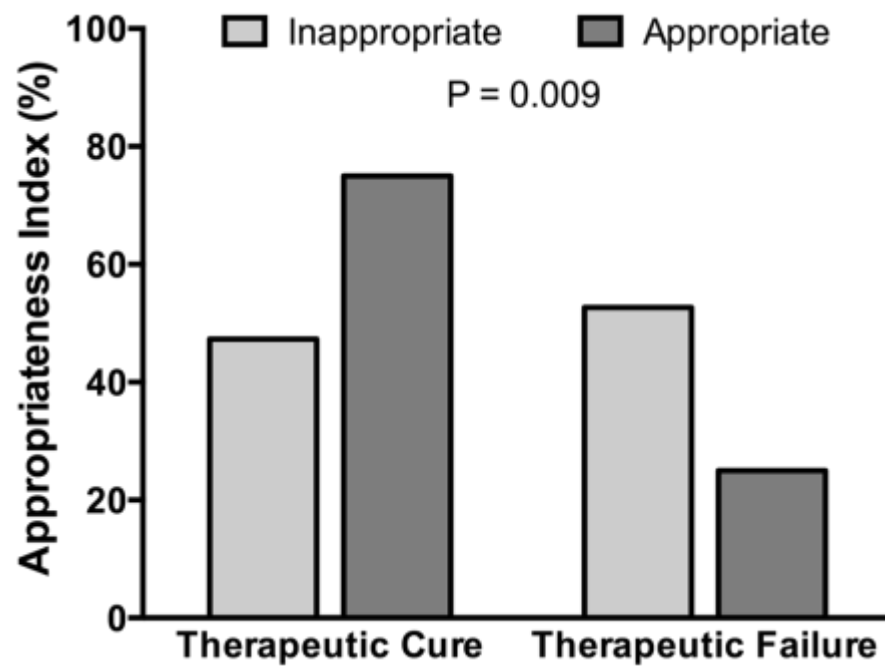


Figure 4: Effect of vancomycin therapeutic drug monitoring on treatment outcomes.

Table 13

*Effect of vancomycin therapeutic drug monitoring service appropriateness on clinical effectiveness*

Appropriateness index (N=208)	Therapeutic cure (N=104)	Therapeutic failure (N=104)	p- value *
] <th colspan="2">n (%)</th> <th></th>	n (%)		
<b>Composite appropriateness of the provided vancomycin TDM service (CA-VTDMS)</b>			
Inappropriate [188 (90.4)]	89 (47.3)	99 (52.7)	0.009
Appropriate [ 20 (9.6)]	15 (75)	5 (25)	
<b>Indication appropriateness</b>			
Inappropriate [47(22.6)]	22 (47)	25 (53)	0.309
Appropriate [161(77.4)]	82 (51)	79 (49)	
<b>Vancomycin blood concentration labeling appropriateness</b>			
Inappropriate [170 (81.7)]	78 (45.9)	92 (54.1)	0.009
Appropriate [38 (18.3)]	26 (68.4)	12 (31.6)	
<b>Sampling time appropriateness relative to the last dose</b>			
<i>Inappropriate ]145 (69.7)]</i>	71(49)	74 (50)	0.381
<i>Appropriate [63 (30.3)]</i>	33 (52)	30 (48)	
<b>Sampling time appropriateness relative to steady-state attainment</b>			
<i>Inappropriate [39 (18.8)]</i>	14 (36)	25 (64)	0.037
<i>Appropriate ]169 (81.3)]</i>	90 (53)	79 (47)	

Table 13

*Effect of vancomycin therapeutic drug monitoring service appropriateness on clinical effectiveness (continued)*

Appropriateness index (N=208)	Therapeutic cure (N=104)	Therapeutic failure (N=104)	p- value*
]n (%)["		n (%)	
<b>Composite sampling time appropriateness</b>			
<i>Inappropriate</i> [147(70.7)[	71 (48)	76 (52)	0.135
<i>Appropriate</i> ]61(29.3)[	33 ( 54)	28 (46 )	
<b>Post-analytical action appropriateness</b>			
<i>Inappropriate</i> ]137 (65.9)[	62 (45)	75 (55)	0.039
<i>Appropriate</i> ]71 (34.1)[	42 (59)	29 (41)	
<b>Composite documentation appropriateness</b>			
<i>Inappropriate</i> [93 (44.7)[	39(40.9)	55 (59.1)	0.013
<i>Appropriate</i> ]115 (55.3)[	66 (57.4)	49 (42.6)	
*Chi-square/Fisher's exact test ; one-sided p-values			

#### 4.1.4.2 Association between vancomycin TDM appropriateness and safety outcomes

The majority of patients who experienced vancomycin-related adverse events received compositely inappropriate vancomycin TDM service [Table 14]. All patients who experienced neutropenia (100%, n=6) received inappropriate vancomycin TDM service. Of all patients who experienced nephrotoxicity, 84.6% (n=11) did not receive compositely appropriate vancomycin TDM service. All-cause mortality occurred in 9 vancomycin TDM recipients, from whom only one patient (11.1%) received a compositely appropriate vancomycin TDM service. Table 14 summarizes the clinical safety and all-cause mortality outcomes pertinent to vancomycin TDM service appropriateness.

Table 14

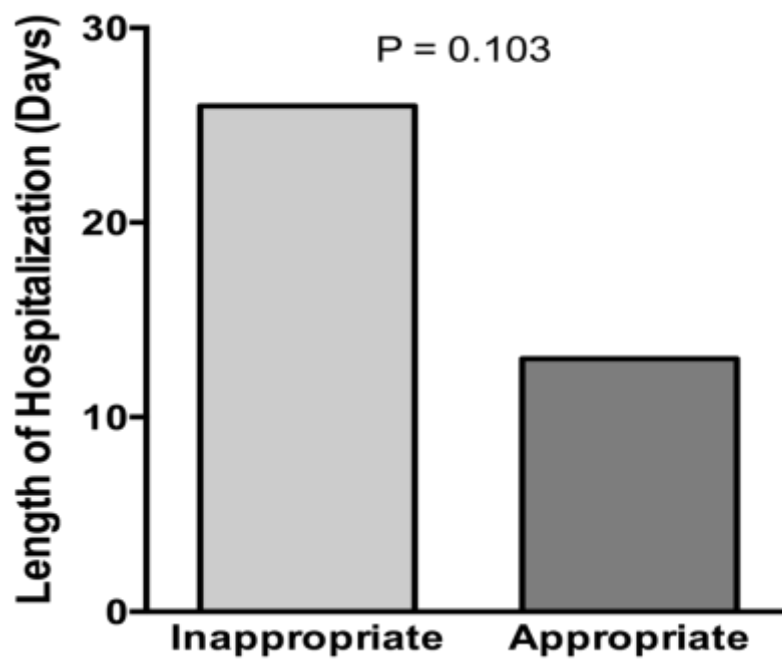
*Association between clinical safety and all-cause mortality outcomes and vancomycin therapeutic drug monitoring service appropriateness*

Clinical endpoint	Composite appropriateness (CA-VTDMS)		p-value*
	Inappropriate <sup>a</sup> (N=91)	Appropriate <sup>b</sup> (N=8)	
[n (%)] <sup>c</sup>	n (%) <sup>c</sup>		
<b>Composite<sup>d</sup> vancomycin-related ADR**</b>			
Yes [19 (19.2)]	17 (89.5)	2 (10.5)	0.403
No [69 (69.7)]	63 (91.3)	6 (8.7)	
<b>Nephrotoxicity**</b>			
Yes [13 (13.1)]	11 (84.6)	2 (15.4)	0.192
No [76 (76.8)]	70 (92.1)	6 (7.9)	
<b>Neutropenia**</b>			
Yes [6 (6.1)]	6 (100)	0 (0)	0.252
No [86 (86.9)]	80 (93)	6 (7)	
<b>All-cause mortality</b>			
Yes [9(9.1)]	8(88.9)	1(11.1)	0.176
No [90 (90.9)]	83 (92.2)	7 (7.8)	

CA-VTDMS: Composite appropriateness of vancomycin TDM service; <sup>a</sup> Number of patients receiving at least one inappropriate CA-VTDMS; <sup>b</sup> Number of patients receiving only appropriate CA-VTDMS; <sup>c</sup> Number of patients; \*Chi-square test was used to compute p-values; \*\*Missing values; <sup>d</sup>Includes both nephrotoxicity and neutropenia

#### 4.1.4.3 Association between vancomycin TDM appropriateness and length of hospitalization

Vancomycin-treated patients who received compositely appropriate vancomycin TDM services compared to those who received inappropriate vancomycin TDM services required shorter hospitalization days by two-fold [median (IQR): 13 (47.7) versus 26 (31) days; p-value=0.103; Figure 5]. Similarly, appropriate post-analytical actions were associated with median shorter hospitalizations by 8.8 days [p-value=0.06]. Conversely, appropriate indication, sampling time relative to steady-state and documentation were significantly associated with longer days of hospitalization [p-value>0.05; Table 15]. Table 15 summarizes length of hospitalization pertinent to vancomycin TDM appropriateness indices.



*Figure 5* : Length of hospitalization pertinent vancomycin therapeutic drug monitoring service appropriateness.



Table 15

*Association between length of hospitalization and vancomycin therapeutic drug monitoring appropriateness indices*

Appropriateness index (N=208)	LOS (days) [median (IQR)]		p-value*
	Inappropriate (N=188)	Appropriate (N=20)	
- Composite appropriateness of vancomycin TDM service (CA-VTDMS)	[26 (31)]	[13 (47.7)]	0.103
- Indication appropriateness	[18 (50)]	[27 (50)]	0.008
- Sampling time appropriateness relative to the last dose (AST-LD)	[24 (31)]	[25.9 (32)]	0.428
- Vancomycin blood concentration labeling appropriateness	[24.5 (31)]	[25.5 (43)]	0.332
- Sampling time appropriateness relative to steady-state attainment (AST-SS)	[13 (11)]	[27 (34)]	<0.001
- Composite sampling time appropriateness (AST-C)	[24 (31)]	[26 (32.6)]	0.475
- Post-analytical action appropriateness (PAA)	[27 (32)]	[18.2 (32)]	0.066
- Composite documentation appropriateness	[18 (21.5)]	[36 (39)]	0.001

LOS: length of hospital stay; \*Mann Whitney *U* test; one-sided p-values

4.2: Phase II: Clinical and Pharmacokinetic Outcomes of the traditional peak-trough-based versus the trough- based vancomycin TDM approaches: A randomized controlled trial

*4.2.1 Baseline demographic, clinical, and pharmacokinetic characteristics of the study participants*

A total of 65 patients were enrolled in the RCT. The trough-only-based vancomycin TDM group (control arm) included 35 patients compared to 30 patients in the peak-trough-based vancomycin TDM group (intervention arm). The baseline characteristics were similar between the study groups [Table 16]. Most of the participants were male (n=52, 80%) and of Asian origin (n=62, 95.4%). Patients presented with CNS infections (n=15, 23.1%), LRTI (n=16, 24.6%), sepsis or septic shock (n=11, 16.9%), bone and joint infections (n=8, 12.3%), SSTI (n=8, 12.3), bacteremia (n=6, 9.2%), intrabdominal infections (n=4, 6.2%) and IE (n=1, 1.5%). Vancomycin was initiated as definitive treatment in more than half of the cases (n=35, 53.3%). Of the identified bacteria (n=35), MRSA (n=17, 48.6%), *S. epidermidis* (n=5, 14.3%) and *E. faecium* (n=4, 11.4%) constituted the most frequent positive microbiologic cultures, warranting definitive vancomycin pharmacotherapy. Approximately half of the study participants were critically-ill and were hospitalized in critical care units (n=31, 47.7%). Physician-prescribed initial vancomycin dosing regimens were comparable between the study groups. Initial peak and trough vancomycin serum concentrations were not therapeutic in 30.2% (n=19) and 80% (n=52) of the cases, respectively [Table-16]. Individual vancomycin clinical

pharmacokinetic parameters (Cl, Vd) were comparable between the study groups. Patients enrolled in peak-trough-based group received the study intervention earlier than trough-only-based group by 0.5 days [p-value, 0.001]. Table 16 summarizes the baseline characteristics of the study participants.

Table 16

*Baseline demographic, clinical, and pharmacokinetic characteristics of randomized controlled trial participants*

Variable <sup>‡,Δ</sup>	Trough- monitoring Group (N=35)	Peak-trough- monitoring Group (N=30)	p- value
<b>Age (years), mean±SD</b>	41.7±19.56	42.4±14.47	0.778
<b>BMI (kg/m<sup>2</sup>), median [IQR]</b>	26.7 [5.2]	25.4 [7.8]	0.969
<i>ABW (kg)</i>	73.1[23.6]	70 [19.3]	0.712
<i>LBW (kg)</i>	64 [9.8]	63.2 [9.8]	0.366
<i>Height (cm)</i>	169 [13]	168 [10.5]	0.597
<b>Gender, n (%)</b>			
<i>Male</i>	30 (85.7)	22 (73.3)	0.213
<i>Female</i>	5 (14.3)	8 (26.7)	
<b>Ethnicity, n (%)</b>			
<i>Asian (Arab)</i>	23 (65.7)	8 (26.7)	0.007
<i>Asian (non-Arab)</i>	11 (31.4)	20 (66.7)	
<i>African</i>	1(2.9)	2 (6.7)	
<b>Hospitalization ward, n (%)</b>			
<i>Intensive care units<sup>‡</sup></i>	13 (37.1)	18 (60)	0.130
<i>Burns unit</i>	2 (5.7)	0 (0)	
<i>Medical ward</i>	11 (31.4)	9 (30)	
<i>Surgical/orthopedic ward</i>	9 (25.7)	3 (10)	

Table 16

*Baseline demographic, clinical, and pharmacokinetic characteristics of randomized controlled trial participants (continued)*

Variable <sup>‡,Δ</sup>	Trough- monitoring Group (N=35)	Peak-trough- monitoring Group (N=30)	P- value
<b>Hospital, n (%)</b>			
<i>HGH</i>	25 (71.4)	21 (70)	
<i>AWH</i>	9 (25.7)	8 (26.7)	0.989
<i>AKH</i>	1 (2.9)	1 (3.3)	
<b>Diagnosis, n (%)</b>			
<i>CNS infection<sup>†</sup></i>	5 (15.3)	10 (33.3)	
<i>Bacteremia</i>	4 (11.4)	2 (6.7)	
<i>Skin and soft tissue infection</i>	4 (11.4)	4 (13.3)	
<i>Bone and joint infection</i>	6 (17.1)	2 (6.7)	0.493
<i>Sepsis/septic shock</i>	5 (14.3)	6 (20)	
<i>Lower respiratory tract infection</i>	7 (20)	5 (16.7)	
<i>Infective endocarditis</i>	1 (2.9)	0 (0)	
<i>Intraabdominal infection</i>	3 (8.6)	1 (3.3)	
<b>Infected physiologic compartment, n(%)</b>			
<i>CNS compartment</i>	5 (14.3)	10 (33.3)	0.339
<i>Blood compartment<sup>Δ</sup></i>	13 (37.1)	9 (30)	
<i>Lung compartment</i>	7 (20)	5 (16.7)	

Table 16

*Baseline demographic, clinical, and pharmacokinetic characteristics of randomized controlled trial participants (continued)*

Variable <sup>‡Δ</sup>	Trough-only- monitoring Group (N=35)	Peak-trough- monitoring Group (N=30)	p- value
<b>Infected physiologic compartment, n(%)</b>			
<i>Other tissues</i> <sup>ΔΔ</sup>	10 (28.6)	6 (20)	
<b>Vancomycin treatment type, n (%)</b>			
<i>Empiric</i>	16 (45.7)	14 (46.7)	0.939
<i>Definitive</i>	19 (54.3)	16 (53.3)	
<b>Positive microbiologic cultures, n (%)</b>			
<i>MRSA</i>	8 (42.1)	9 (56.3)	0.313
<i>MSSA</i>	5 (26.3)	3 (18.6)	
<i>S. epidermidis</i>	4 (21.1)	1 (6.3)	
<i>S. constellatus</i>	1 (5.3)	0 (0)	
<i>E. faecium</i>	1 (5.3)	3 (18.8)	
<b>Baseline vancomycin treatment details</b>			
<i>Dose (mg/dose), median [IQR]</i>	1000 [0]	1000 [0]	0.682
<i>Dose (mg/kg/dose), median [IQR]</i>	14.3 [5.6]	14.6 [3.7]	0.531
<i>Total daily dose (mg/day), median [IQR]</i>	2000 [1000]	2000 [125]	0.359
<i>Total daily dose (mg/kg/day), median [IQR]</i>	28.6 [16.5]	29.2 [7.4]	0.864

Table 16

*Baseline demographic, clinical, and pharmacokinetic characteristics of randomized controlled trial participants (continued)*

Variable †,Δ	Trough-only- monitoring Group (N=35)	Peak-trough- monitoring Group (N=30)	p- value
<b>Baseline vancomycin treatment details</b>			
<i>Cumulative doses received (mg), median [IQR]</i>	4000 [1250]	5000 [2063]	0.042
<i>Cumulative doses received (mg/kg), median [IQR]</i>	59.4 [25.04]	66.8 [29.6]	0.049
<i>Pre-enrollment days on vancomycin treatment, median[IQR]</i>	2 [0.5]	1.5 [1]	0.001
<b><i>Dosing interval, n(%)</i></b>			
<i>Q 6 hr</i>	2 (5.7)	1 (3.3)	
<i>Q 8 hr</i>	10 (28.6)	3 (10)	0.141
<i>Q 12 hr</i>	23 (65.7)	26 (86.7)	
<b><i>Infusion duration , n (%)</i></b>			
<i>Infused over 0.5 hr</i>	1 (2.9)	0 (0)	
<i>Infused over 1 hr</i>	32 (91.4)	29 (96.7)	0.576
<i>Infused over 1.5 hr</i>	2 (5.7)	1 (3.3)	

Table 16

*Baseline demographic, clinical, and pharmacokinetic characteristics of randomized controlled trial participants (continued)*

Variable ‡,Δ	Trough-only- monitoring Group (N=35)	Peak-trough- monitoring Group (N=30)	p- value
<b>Pharmacokinetic parameters at treatment initiation</b>			
<i>V<sub>d</sub> (L), mean±SD</i>	48.5±10.7	51.14±9.96	0.311
<i>K<sub>e</sub> (hr<sup>-1</sup>), mean±SD</i>	0.094±0.05	0.089±0.051	0.702
<i>Cl (L/hr), mean±SD</i>	4.15±2.22	4.24±2.20	0.861
<i>t<sub>1/2</sub> (hr), median[IQR]</i>	8.01 [11.12]	7.23 [9.75]	0.722
<i>CrCl (L/hr), median[IQR]</i>	6.51 [3.44]	6.45 [3.12]	0.374
<i>AUC per dose (mg.hr/L), median[IQR]</i>	226.94[195.6]	228.30 [273.01]	0.590
<b>Initial vancomycin serum concentrations , (mg/L), median[IQR]</b>			
<i>Trough-1</i>	9 [8.3]	8.4 [12.9]	0.732
<i>Peak</i>	25 [10]	27.9 [17.8]	0.863
<i>Random-1</i>	18.9 [9.4]	18 [18.1]	0.837
<i>Random-2</i>	11.9 [8.7]	11.1 [13.28]	0.638
<i>Trough-2</i>	10.6 [10.5]	8.9 [15.1]	0.844
<b>Interpretation of initial peak vancomycin concentrations, n (%)*</b>			
<i>Therapeutic</i>	27 (77.1)	17 (60.7)	0.158
<i>Non-therapeutic</i>	8 (22.9)	11 (39.3)	



Table 16

*Baseline demographic, clinical, and pharmacokinetic characteristics of randomized controlled trial participants (continued)*

Variable <sup>‡,Δ</sup>	Trough-only- monitoring Group (N=35)	Peak-trough- monitoring Group (N=30)	P- value
<b>Interpretation of initial trough vancomycin concentrations, n (%)</b>			
<i>Therapeutic</i>	6 (17.1)	7 (23.3)	
<i>Non-therapeutic</i>	29 (82.9)	23 (76.7)	0.534
<b>Laboratory parameters</b>			
<i>White blood cells (x10<sup>9</sup>IU/l), mean±SD</i>	13.36±7.9	12.8±6.02	0.958
<i>Hemoglobin (g/dL), median [IQR]</i>	11.53 [2.32]	11.7 [4.15]	0.350
<i>Lymphocytes (x10<sup>9</sup>IU/L), median [IQR]</i>	1.4 [1.2]	1.45 [1.43]	0.594
<i>Neutrophils(x10<sup>9</sup>IU/L) , median [IQR]</i>	8 [9.8]	8.2 [7.7]	0.974
<i>Eosinophils (x10<sup>9</sup>IU/L), median [IQR]</i>	0.1 [0.2]	0.1 [0.3]	0.924
<i>Basophils (x10<sup>9</sup>IU/L), median [IQR]</i>	0.03 [0.07]	0.03 [0.05]	0.327
<i>SCr(μmol/L), median [IQR]</i>	65 [36]	67 [30]	0.347
<i>Albumin (g/L), median [IQR]</i>	29 [12]	28.5 [14.3]	0.983
<i>ALT (IU/L), median [IQR]</i>	35.5 [44]	28.5 [22]	0.120
<i>AST(IU/L), median [IQR]</i>	43 [64]	37.5 [39]	0.309
<i>ALP (IU/L), median [IQR]</i>	104 [84]	92 [93]	0.586
<i>Glucose(mmol/L), median [IQR]</i>	6.45 [2.32]	6.2 [1.95]	0.852

Table 16

*Baseline demographic, clinical, and pharmacokinetic characteristics of randomized controlled trial participants (continued)*

Variable <sup>‡,Δ</sup>	Trough-only- monitoring Group (N=35)	Peak-trough- monitoring Group (N=30)	p- value
<b>Concomitant antibiotics, n (%)</b>	18 (51.4)	22 (55)	0.070
<i>Beta-lactams</i>	9 (25.7)	9 (30)	0.347
<i>Carbapenems</i>	10 (15.4)	11 (16.9)	0.487
<i>Cephalosporins</i>	9 (25.7)	12 (40)	0.220
<i>Clindamycin</i>	2 (5.7)	1 (3.3)	0.648
<i>Linezolid</i>	0 (0)	4 (13.3)	0.026
<i>Rifampicin</i>	1 (2.9)	1 (3.3)	0.912
<b>Concomitant nephrotoxic agents, n (%)</b>	12 (34.3)	12 (40)	0.634
<i>Amphotericin B</i>	0 (0)	2 (6.7)	0.121
<i>NSAIDs</i>	8 (22.9)	10 (33.3)	0.347
<i>ACEI/ARBs</i>	4 (11.1)	1 (3.3)	0.222
<i>Loop/thiazide diuretics</i>	4 (11.4)	6 (20)	0.340
<i>Acyclovir</i>	1 (2.9)	0 (0)	0.351
<b>Concomitant medical conditions, n(%)</b>			
<i>Diabetes mellitus</i>	6 (17.1)	8 ( 26.7)	0.352
<i>Chronic kidney disease</i>	1 (2.9)	2 (6.7)	0.466

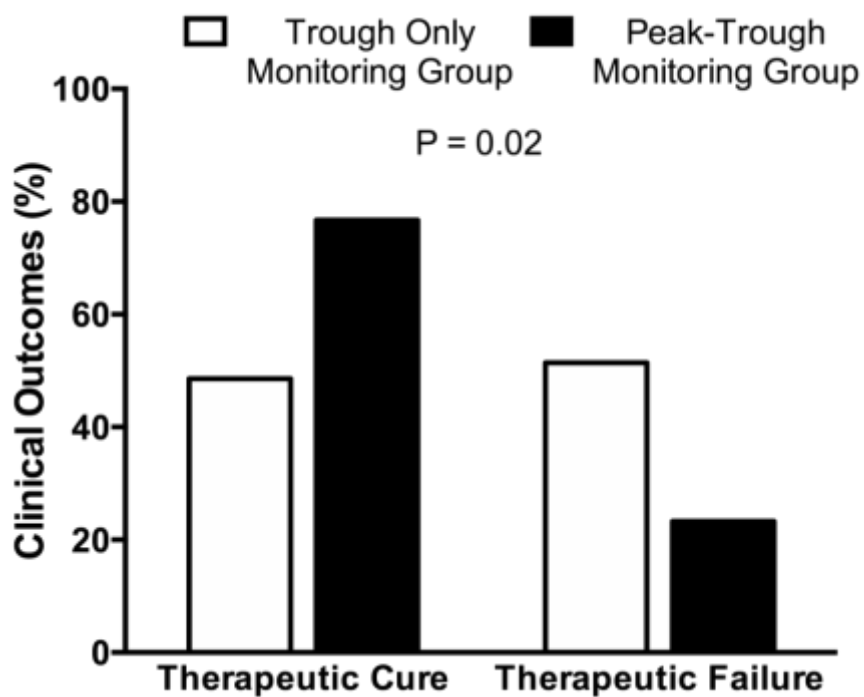
Table 16

*Baseline demographic, clinical, and pharmacokinetic characteristics of randomized controlled trial participants (continued)*

Variable <sup>‡,Δ</sup>	Trough-only- monitoring Group (N=35)	Peak-trough- monitoring Group (N=30)	p- value
<b>Concomitant medical conditions, n(%)</b>			
<i>Hypertension</i>	7 (20)	11 (36.7)	0.134
<i>Coronary vascular disease</i>	2 (5.7)	4 (13.3)	0.290
<i>Heart failure</i>	1 (2.9)	2 (6.7)	0.466
BMI: body mass index; ABW: actual body weight; ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; Hgb: hemoglobin; LBW: lean body weight; MRSA: methicillin-resistant staphylococcus aureus, MSSA: methicillin-sensitive staphylococcus aureus; <sup>‡</sup> Involves meningitis, encephalitis and ventriculitis; <sup>‡</sup> Includes trauma, medical and surgical intensive care units; <sup>Δ</sup> Includes blood, intrabdominal and cardiac infections; <sup>ΔΔ</sup> Includes skin, soft tissue, bone and joint infections; *Missing values			

#### *4.2.2 Clinical outcomes of peak-trough-based versus trough-only-based vancomycin TDM approaches*

Peak-trough-based vancomycin TDM was significantly associated with higher infection cure rates compared to trough-only based vancomycin TDM [76.7% versus 48.6%; p-value=0.02; Table 17; Figure 6]. Compared to the control group (trough-only-based group), the intervention group (peak- trough-based group) required median shorter durations of vancomycin treatment and hospitalization by 0.5 days and 4.5 days, respectively [p- value>0.05; Table 17]. Trough-only-based vancomycin TDM was associated with 4.8-fold more therapeutic failures compared to peak-trough-based vancomycin TDM [p-value=0.02; Table 17]. No statistically significant differences were observed for all-cause mortality, neutropenia and nephrotoxicity between the two monitored groups [p-value>0.05; Table 17]. Table 17 summarizes the therapeutic outcomes associated with peak-trough- based versus trough-only-based vancomycin TDM approaches.



*Figure 6* : Clinical outcomes of peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring approaches.

Table 17

*Clinical outcomes of peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring approaches*

Variable	Trough-only-	Peak-trough-	P-value*
	monitoring Group‡ (N=35)	monitoring Group¥ (N=30)	
Vancomycin treatment efficacy outcomes, n (%)			
<i>Therapeutic cure</i>	17 (48.6)	23 (76.7)	0.020
<i>Therapeutic failure</i>	18 (51.4)	7 (23.3)	
Vancomycin treatment safety outcomes, n (%)			
<i>Neutropenia</i>	3 (8.6)	1 (3.3)	0.381
<i>Nephrotoxicity</i>	1 (2.9)	1 (3.3)	0.912
All-cause mortality, n(%)	3 (8.6)	2 (6.7)	0.774
Length of hospitalization (days), median [IQR]	20 [25]	15.5 [22]	0.320
Total duration on vancomycin treatment (days), median [IQR]	7 [10]	6.5 [7.3]	0.319

\*Chi-square test or Mann-Whitney-*U* test

#### *4.2.3 Clinical pharmacokinetic outcomes of peak-trough-based versus trough-only-based vancomycin TDM approaches*

Vancomycin dosing requirements significantly differed between the compared vancomycin TDM approaches, with the trough-only group having significantly higher doses [p-value<0.05; Figure 7; Table 18]. Compared to the trough-only-based vancomycin TDM group, the peak-trough-based group required lower average vancomycin single doses and total daily doses by 370 mg/dose and 927 mg/day, respectively [p-value <0.05; Table 18]. Despite the similar duration on vancomycin treatment between the study groups, trough-only-based vancomycin TDM recipients received statistically significantly higher median cumulative vancomycin doses by 6250mg [p-value> 0.05; Table 18]. More importantly, patients receiving trough-only-based vancomycin TDM required a median of at least 2 dose adjustments to achieve target serum concentrations for the first time compared to the intervention group who achieved therapeutic concentrations from the first dosage adjustment episode in most instances [median (IQR):1(1); p-value>0.05; Table 18]. Also, trough-only based monitoring was associated with recommended vancomycin dosing regimens of lower dosing frequencies and larger single doses, necessitating longer infusion durations that exceeded 1 hour compared to peak-trough-based doses [p-value>0.05; Table 18]. Compared to trough-only-based vancomycin doses, AUCs per single dose and 24-hr AUCs were less with peak-trough-based doses by approximately 50 mg.hr/L [p-value>0.05; Table 18]. The compared TDM approaches resulted in statistically and clinically significant different peak

concentrations; peak-trough-based vancomycin dose adjustments compared to trough-only based vancomycin dose adjustments resulted in achievement of target peaks 94.1% versus 69% of the times, respectively [p-value=0.006; Table 18]. Interestingly, peak-trough-based vancomycin doses resulted in higher rates of therapeutic troughs compared to trough-only based vancomycin doses [p-value>0.05; Table 18].



Table 18

*Clinical pharmacokinetic outcomes of peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring approaches*

Variable	Trough-only- monitoring Group (N=35)	Peak-trough- monitoring Group (N=30)	P- value
<b>Vancomycin doses received</b>			
<i>Dose (mg/dose), mean ±SD</i>	1385.71±530.62	1015±332.221	0.001
<i>Dose (mg/kg/dose), mean ±SD</i>	19.03±7.76	14.09±5.68	0.005
<i>Total daily dose (mg/day), mean ±SD</i>	3834.49±1362.83	2907±1416.08	0.009
<i>Total daily dose (mg/kg/day), mean ±SD</i>	52.83±21.59	40.78±21.25	0.027
<i>Cumulative doses received (mg), median [IQR]</i>	19500 [25860]	13250[14925]	0.192
<b>Vancomycin dosing interval, n (%)</b>			
<i>Q 6 hr</i>	6 (17.1)	11 (36.7)	0.091
<i>Q 8 hr</i>	16 (45.7)	12 (40)	
<i>Q 12 hr</i>	13 (37.1)	4 (13.4)	
<i>Q 18 hr</i>	0 (0)	1 (3.3)	
<i>Q 24 hr</i>	0 (0)	1 (3.3)	
<i>Q 36 hr</i>	0 (0)	1 (3.3)	

Table 18

*Clinical pharmacokinetic outcomes of peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring approaches (continued)*

Variable	Trough-only-	Peak-trough-	P-
	monitoring	monitoring	
	Group	Group	value
	(N=35)	(N=30)	
<b>Vancomycin infusion duration, n (%)</b>			
<i>Infused over 0.5 hr</i>	1 (2.9)	0 (0)	
<i>Infused over 1 hr</i>	19 (54.3)	22 (73.3)	
<i>Infused over 1.5 hr</i>	10 (28.5)	8 (26.7)	0.297
<i>Infused over 2.5 hr</i>	2 (5.7)	0 (0)	
<i>Infused over 3 hr</i>	2 (5.7)	0 (0)	
<i>Infused over 4 hr</i>	1 (2.9)	0 (0)	
Minimum number of dose adjustments required to first therapeutic serum concentrations, median[IQR]	2 [2]	1 [1]	0.105
Post-dose adjustment peak concentration (mg/L), mean±SD	35.94±7.7	30.38±5.17	0.021
Post-dose adjustment trough concentration (mg/L), mean±SD	16.8±3.09	15.6±3.49	0.596

Table 18

*Clinical pharmacokinetic outcomes associated with peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring approaches*  
(continued)

Variable	Trough-only-	Peak-trough-	P- value
	monitoring Group (N=35)	monitoring Group (N=30)	
<b>Interpretation of post-dose adjustment peak concentrations †, n (%)*</b>			
<i>Therapeutic</i>	29 (69)	32 (94.1)	
<i>Subtherapeutic</i>	13 (31)	2 (5.9)	0.006
<i>Supratherapeutic</i>	0 (0)	0 (0)	
<b>Interpretation of post-dose adjustment trough concentrations, n(%)<sup>†‡</sup></b>			
<i>Therapeutic</i>	25 (44.6)	20 (54.1)	
<i>Subtherapeutic</i>	19 (33.9)	10 (27)	0.665
<i>Supratherapeutic</i>	12 (21.4)	7 (18.9)	
AUC per dose (mg.hr/L), median[IQR]	269.54 [156.02]	223.46 [168.82]	0.590
24-hr AUC (mg.hr/L), median [IQR]	771.76 [412.95]	708 [260.87]	0.762
†56 dose adjustments applied; ‡ 37 dose adjustments applied ; *Missing values			

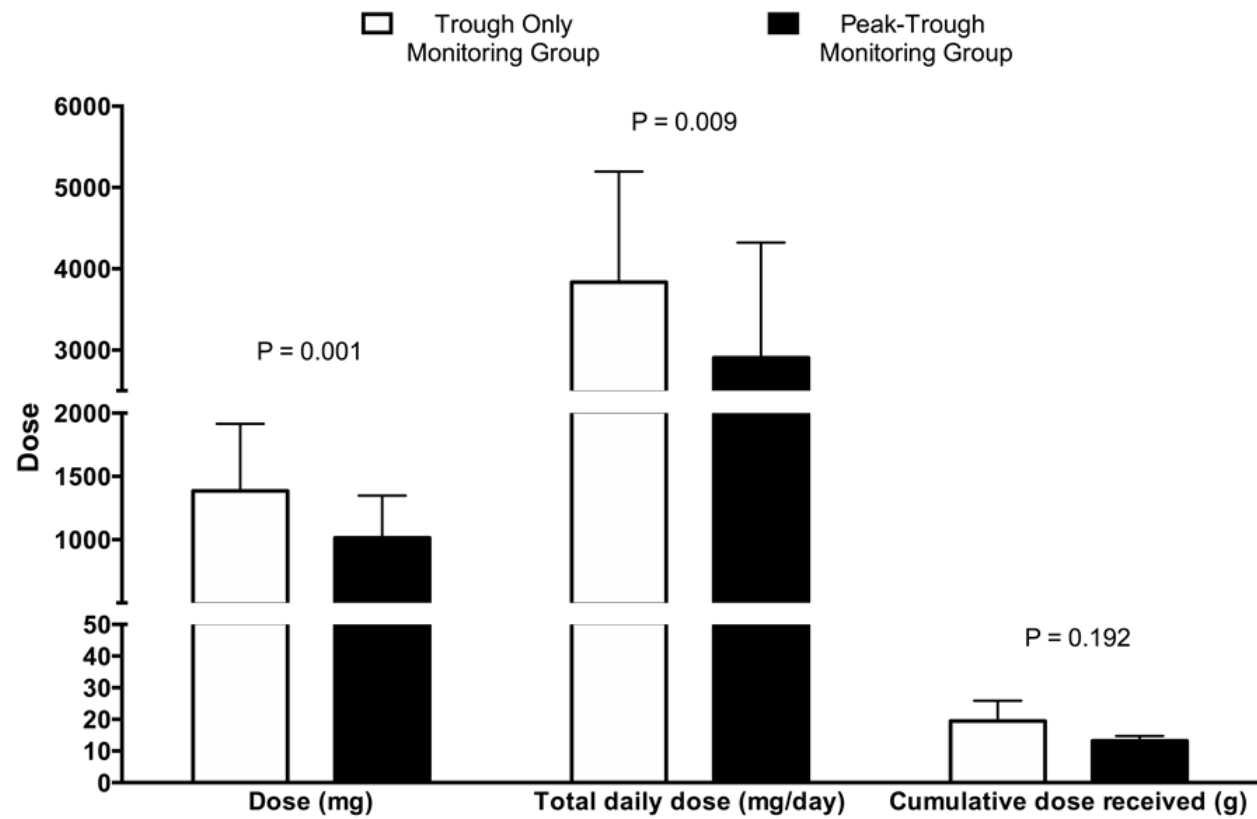


Figure 7 : Vancomycin dosing requirements of peak-trough-based versus trough-only-based vancomycin therapeutic drug monitoring recipients.

#### 4.2.4 Association between vancomycin AUCs and cure

To determine the 24-hr AUC that was best associated with therapeutic cure, CART modeling was conducted. In Model-0, 24-hr AUC was modelled as the only independent variable to predict cure, and included all the study participants (empiric and definitive vancomycin treatment recipients). CART identified a 24-hr AUC of less than or equal 863.97 mg.hr/L to best correlate with therapeutic success rates [70.2%, n=33; Figure 8]. Model-0 correctly predicted therapeutic outcome in 67.7% of the cases [Table 19]. To confirm this, Model-1 included only cases that received vancomycin as definitive treatment [Figure 9]. Similar to Model-0, Model-1 identified a 24-hr AUC not exceeding 796.76 mg.hr/L to best correlate with cure [75%, n=18; Figure 5] with comparable predictive performance [Table 19].

To improve the predictive performance of the generated models, more independent variables were explored. In Models 2 and 3, the number of days on vancomycin treatment before receiving vancomycin TDM, infected physiologic compartment, ethnicity, CrCl and vancomycin TDM approach (peak-trough-based versus trough-only-based TDM) were tested against cure in CART [Figure 10 & 11]. When definitive and empiric vancomycin treated cases were included (Model-2), CART identified CrCl less than 7.85 L/hr to be the highest variable correlated with cure rates [76.1%, n=35]. A second split occurred at 24-hr AUC  $\leq$  1255.98 mg.hr/L, where 86.1% (n=31) cure rates were observed. All patients who achieved 24-hr AUC  $\leq$  1255.98 mg.hr/L and received peak-trough-based vancomycin TDM achieved clinical success rates [100%, n=19; Figure-10]. Contrastingly, patients who maintained 24-hr

AUC $\leq$ 1255.98 mg.hr/L, but received trough-only-based vancomycin TDM experienced 29.4% (n=5) failure rates. Maintenance of 24-hr AUC  $>$ 564.117 mg.hr/L was identified to be correlated with cure in trough-only-based TDM recipients [84.6%, n=11; Figure 10]. To confirm these findings, Model-3 was generated [Table 19; Figure 11]. Model-3 included definitive vancomycin-treated cases only (n=35) and confirmed the findings from Model-2. The predictive performance of Models 2 and 3 was high with low misclassification risks [Table 19]. Models 2 and 3 correctly predicted outcomes in 86.2% and 100% of the times, respectively. Upon cross-validation, Models 2 and 3 showed an outcome misclassification risk not exceeding 32%, suggesting robustness [Table 19]. CART identified CrCl, 24-hr AUC and the type of vancomycin TDM approach as significant determinants of therapeutic outcomes with 100%, 58.4% and 45.8% normalized importance to the model, respectively [Figure 12].

Table 19

*Predictive performance of generated classification and regression trees (CART) models*

Model name	Figure reference	Correct predictions			Misclassification risk	
		Cure	Failure	Overall	Resubstitution	Cross-validation Estimate
		N (%)	N (%)	N (%)	Estimate [ SE]	[SE]
Model 0 <sup>Δ</sup>	Fig.8	33 (82.5)	11 (44)	44 (67.7)	0.323 [0.058]	0.400 [0.061]
Model 1 <sup>‡</sup>	Fig 9	18 (78.3)	6 (50)	24 (68.6)	0.314 [0.078]	0.543 [0.084]
Model 2 <sup>Δ</sup>	Fig.10	33 (82.5)	23 (92)	56 (86.2)	0.138 [0.043]	0.323 [0.058]
Model 3 <sup>‡</sup>	Fig.11	19 (82.6)	12 (100)	31 (100)	0.114 [0.054]	0.286 [0.076]

<sup>Δ</sup>N=65; Empiric and definitive indications for vancomycin treatment

<sup>‡</sup>N=35; Definitive indications for vancomycin treatment

SE: Standard error

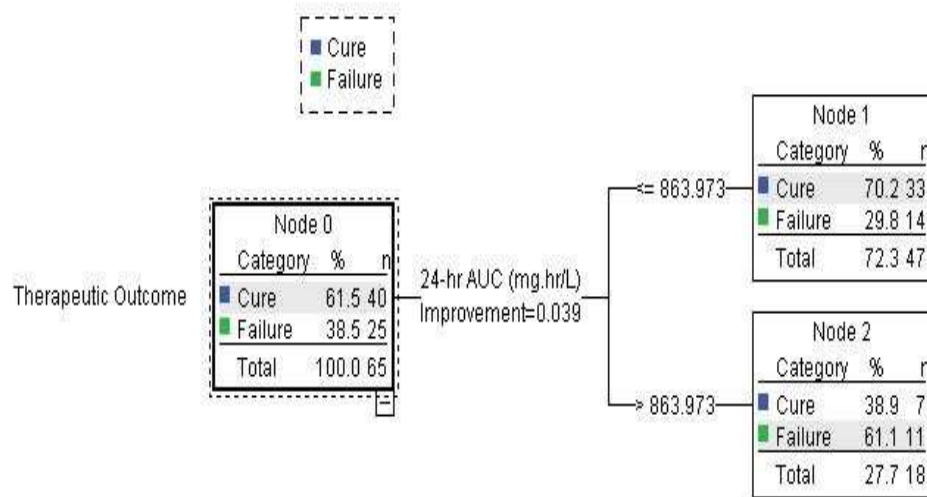


Figure 8: Association between vancomycin 24-hr AUC and therapeutic outcomes in empiric and definitive vancomycin-treated infections.

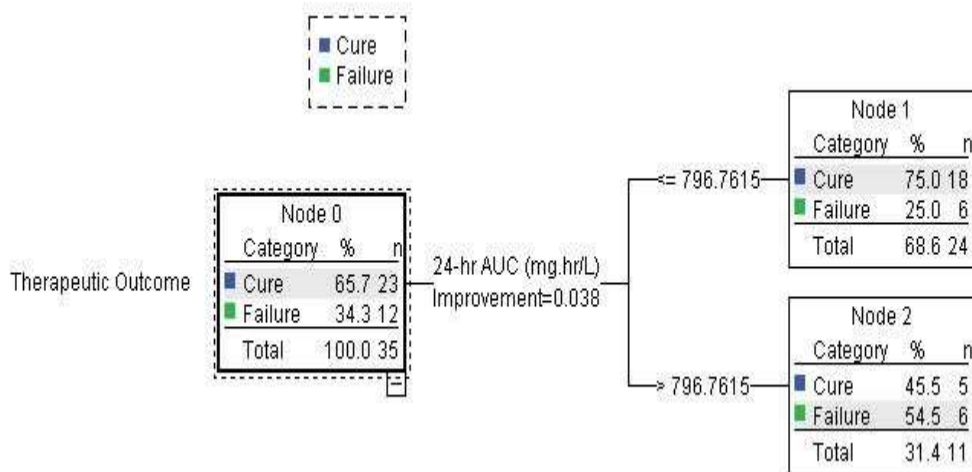


Figure 9: Association between vancomycin 24-hr AUC and therapeutic outcomes in definitive vancomycin-treated infections.



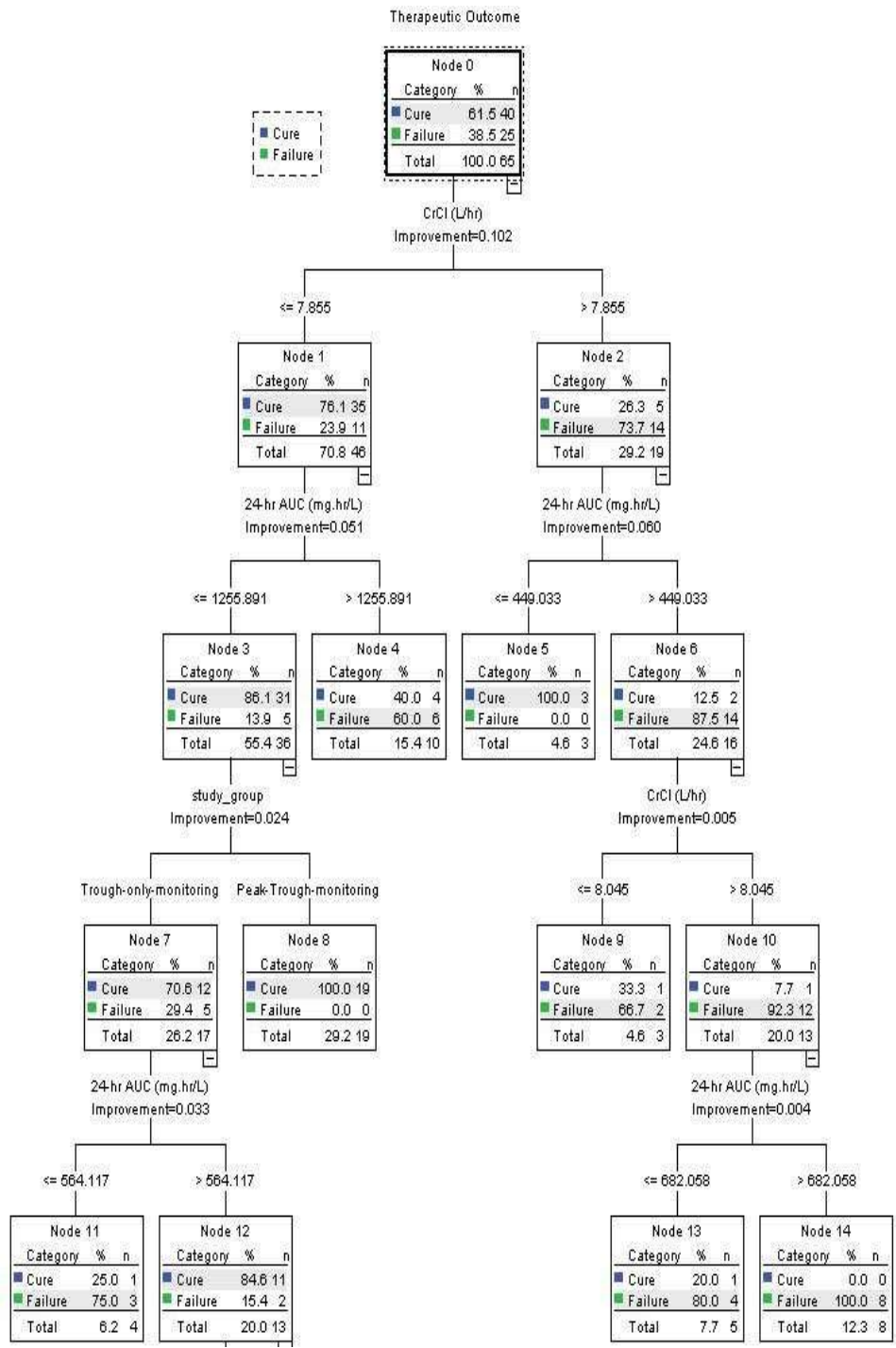


Figure 10: Relationship between vancomycin 24-hr AUC, TDM approach, CrCl and therapeutic outcomes in empiric and definitive vancomycin-treated infections.

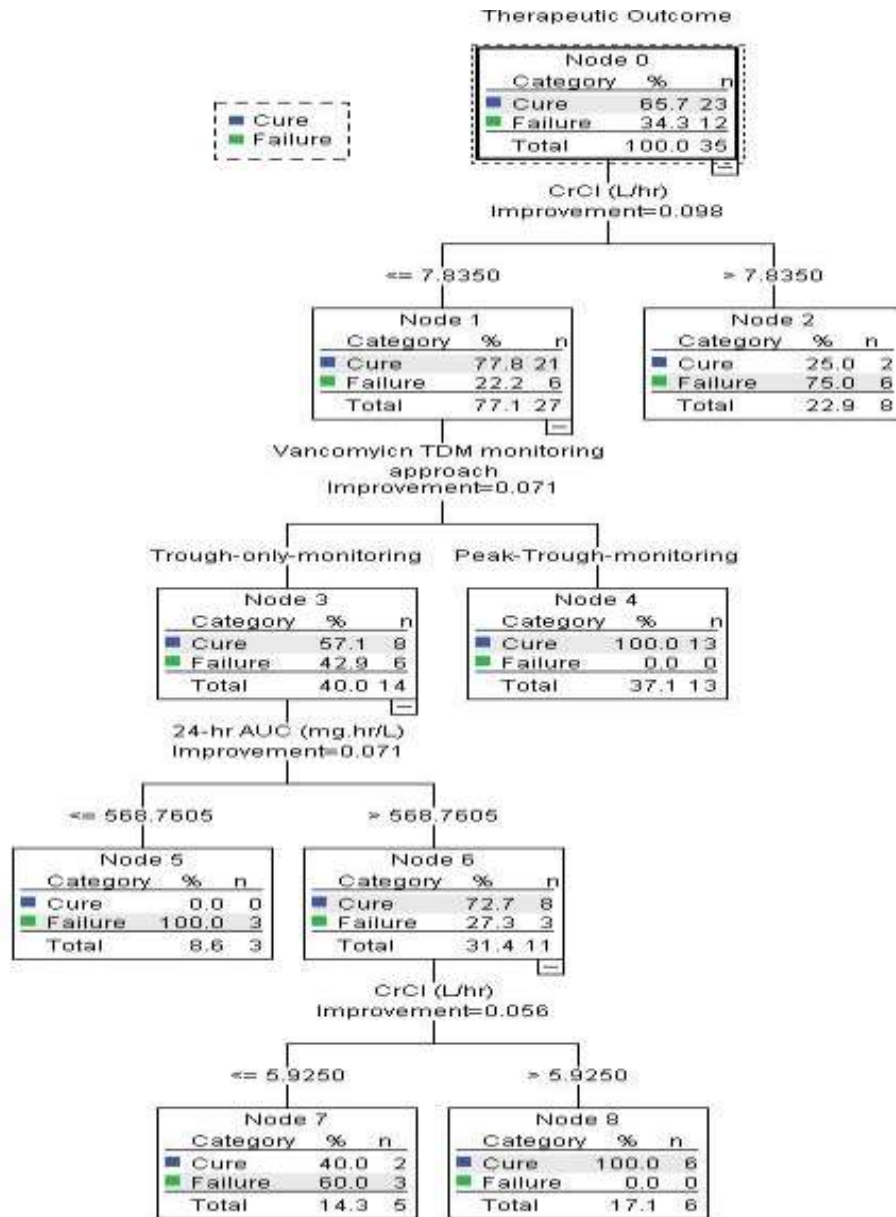
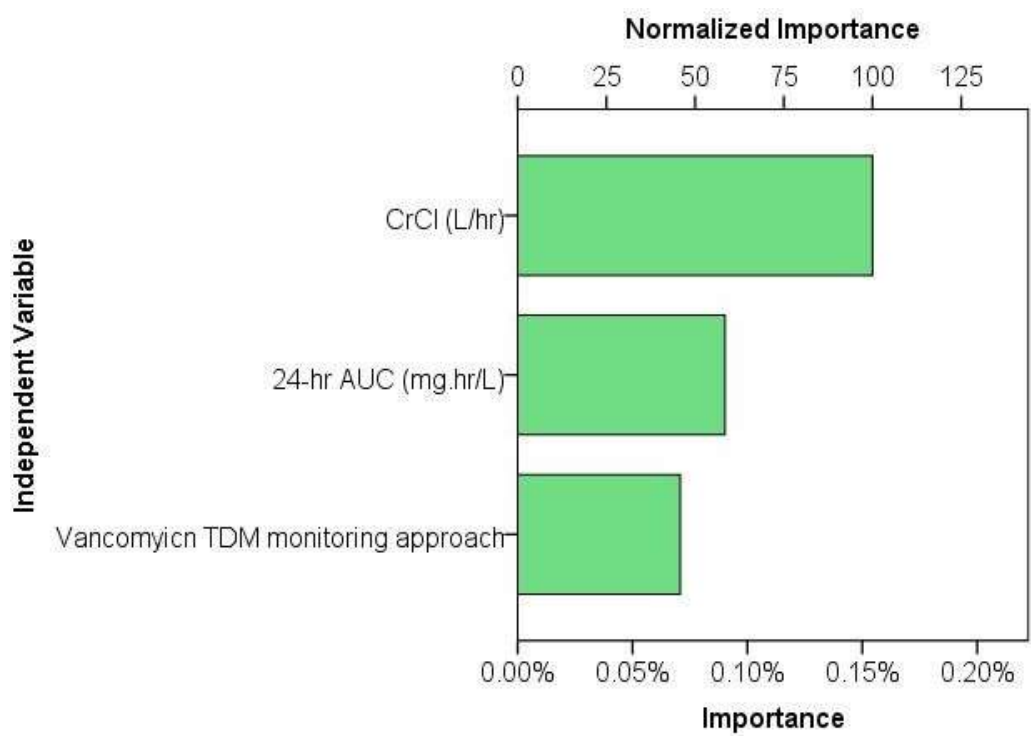


Figure 11: Relationship between vancomycin 24-hr AUC, TDM approach and CrCl and therapeutic outcomes in definitive vancomycin-treated infections.



*Figure 12:* Relative importance of CART identified independent variables as determinants of therapeutic outcomes with vancomycin treatment.

### 4.3 Phase III: Vancomycin Population Pharmacokinetics

#### *4.3.1 Base model*

A total of 769 vancomycin blood concentrations obtained from 156 patients were analyzed. A two-compartment structural model with a proportional residual error and BSV modeled on Cl, Vc and Q best described vancomycin disposition in the studied population (OFV of 3255.281). Compared to the two-compartment model, a one-compartment model resulted in significantly higher OFV by 131.252 units. Our data set failed minimization with a three-compartment structural model. Modeling study site, or visit number on residual error model did not result in significant decrease in OFV. Yet, modeling study group (prospective vs. retrospective cohorts) on RUV resulted in a decrease in the OFV by 29.461 units (OFV=3225.820; RSE=270%; 95% CI: -13%-15.7%). Due to the high %RSE (270%), this decrease was considered artificial and thus it was decided to exclude the study group from the stochastic model. PK parameter estimates from the base model showed acceptable precision (RSE<30%), but relatively high between subject variability ( $\omega_{Cl}$ = 66.71%,  $\omega_{Vc}$  66.56%). Table 20 summarizes vancomycin parameter estimates from the base model.

Table 20

*Base model estimated vancomycin population pharmacokinetic model parameters*

Parameter	EBE <sup>¥</sup>	RSE <sup>€</sup> (%)	95% CI*
<b>Fixed parameters</b>			
Cl (L/hr)	4.59	6.01	4.05-5.13
V <sub>c</sub> (L)	55.2	9.55	44.9-65.5
V <sub>p</sub> (L)	64.5	29.8	26.9-102
Q (L/hr)	1.75	21.2	1.02-2.48
<b>Between subject variability (CV%)</b>			
$\omega_{Cl}$	66.71	17.3	54.22-77.2
$\omega_{Vc}$	66.56	43.3	25.82-90.49
$\omega_{Vp}$	-	-	
$\omega_Q$	87.01%	34.1	50.09-112.25
<b>Residual unexplained variability (CV%)</b>			
Proportional $\sigma$	20.34	11.6	17.89-22.54

<sup>¥</sup>Post-hoc empirical Bayes estimates (EBE); <sup>€</sup>Relative standard error = (standard error / EBE) x 100; \*95% confidence intervals; **CV**: coefficient of variation; Cl: clearance of vancomycin; V<sub>c</sub>: volume distribution of vancomycin in the central compartment; Q: intercompartmental clearance of vancomycin; V<sub>p</sub>: volume of distribution of vancomycin in the peripheral compartment;  $\omega$ : between subject variability related to PK parameter;  $\sigma$ : residual unexplained variability, including within-subject variability

#### *4.3.2 Covariate model*

Covariates were tested against clinically relevant (Cl, Vc) vancomycin PK parameters. Visual plots showed no obvious trends in relationships between Cl or Vc with AST, ALT, WBC, race, gender, or physiologic compartment of the infection [Figures 13 and 10; some plots not shown]. Lean body weight (LBW), total body weight (TBW), age and CrCl showed some trends in relationships with vancomycin Cl [Figure 13]. Covariate plots showed possible relationships of Vc with Age, LBW, BSA, TBW [Figure 14]. These relationships were objectively tested in forward selection-backward elimination procedures [Table 21].

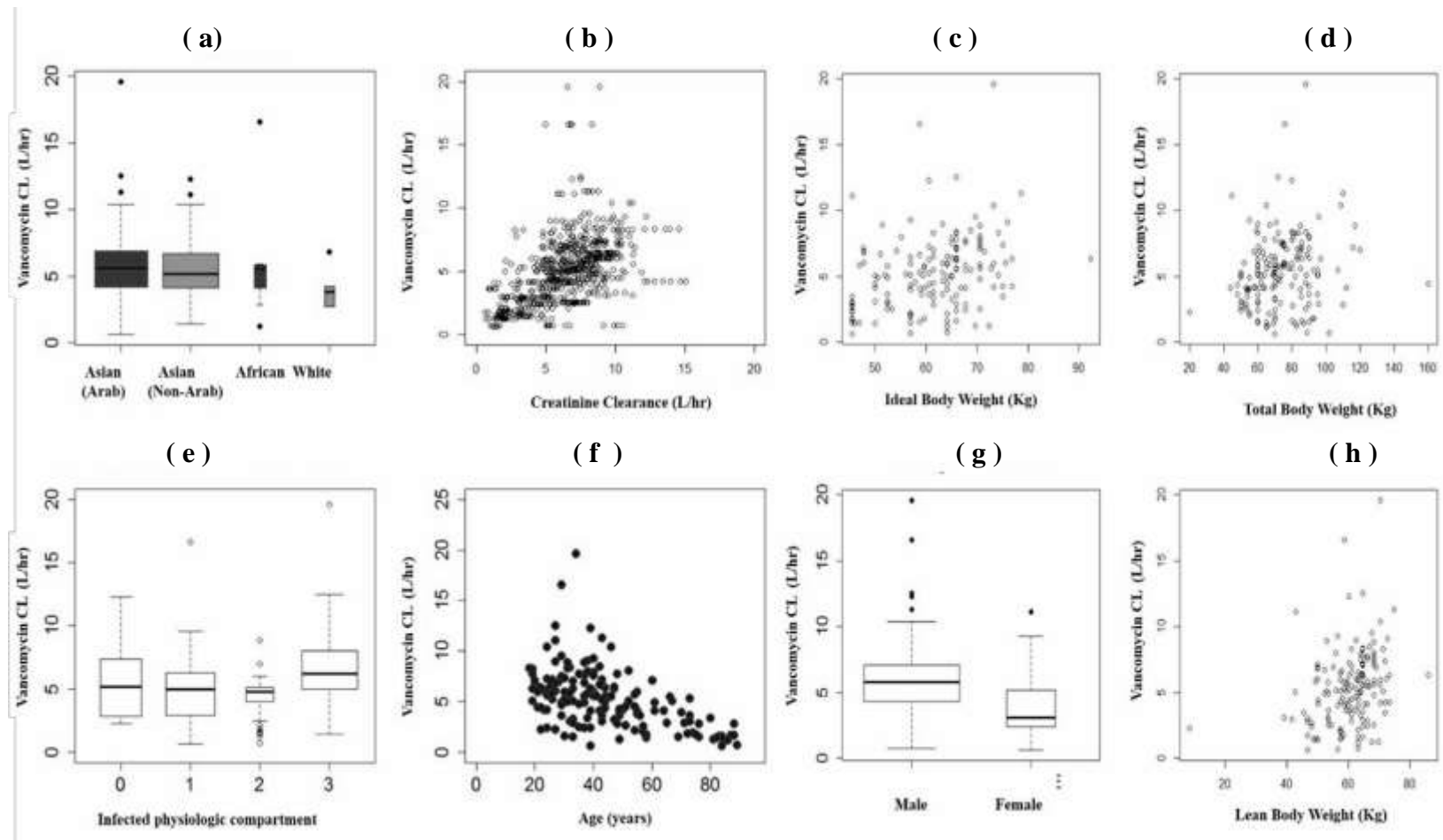


Figure 13: Covariate relationships with vancomycin clearance (Cl).

e) Infected physiologic compartment; 0: CNS; 1: systemic blood ; 3: respiratory; 4: skin, soft tissues, bone and joints;

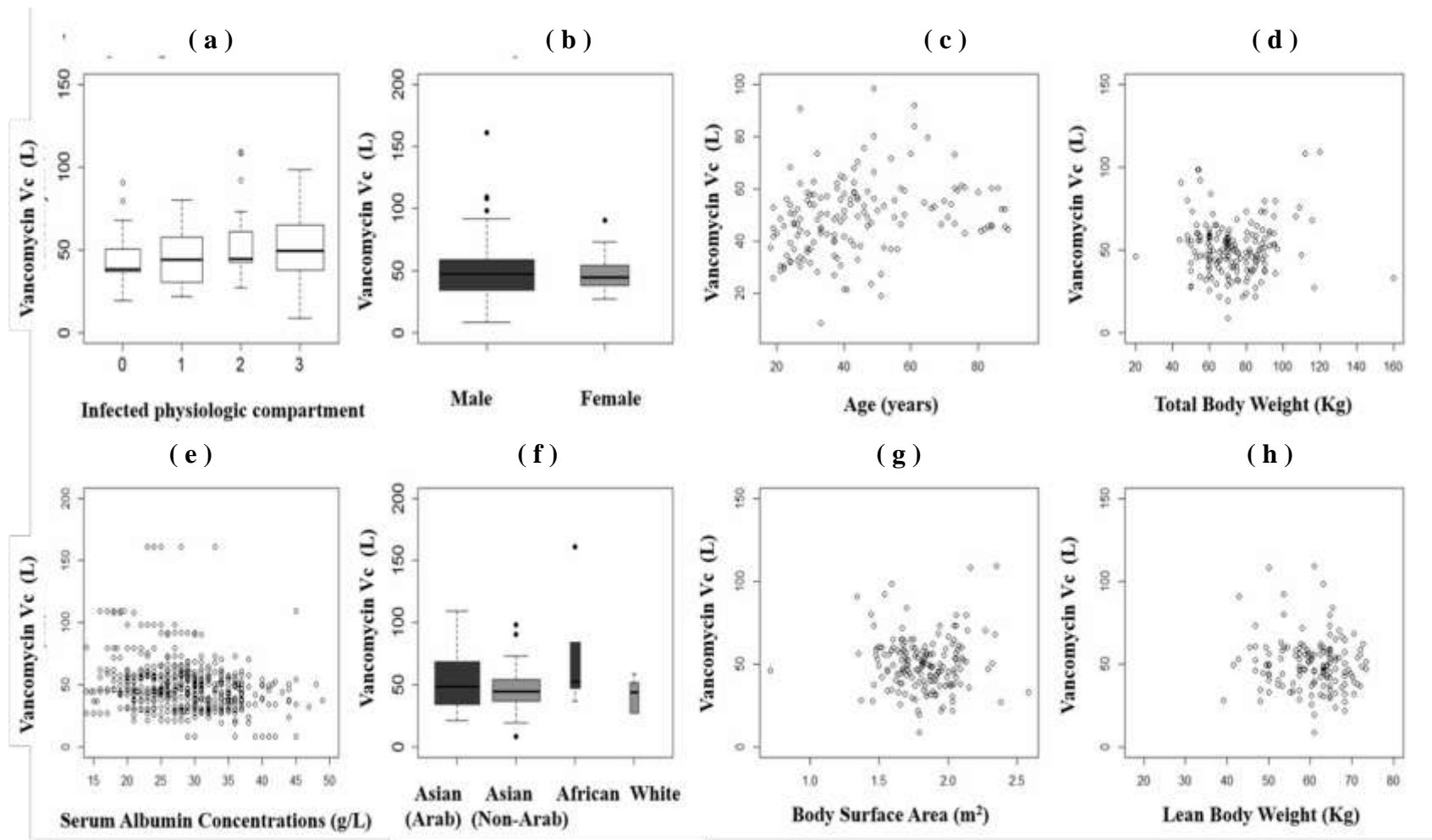


Figure 14: Covariate relationships with vancomycin volume of distribution in central compartment (Vc).

a) Infected physiologic compartment-Vc; 0: CNS; 1: systemic blood ; 3: respiratory; 4: skin, soft tissues, bone and joints;



During univariate covariate testing, the addition of CrCl on vancomycin clearance resulted in the most significant improvement in OFV by 108.552 units (p-value<0.05). During multivariate analysis, adding age on Vc resulted in an additional significant drop in OFV by 6.262 units (p-value <0.05). Backward elimination results proved CrCl as a significant covariate on Cl as excluding it from the model significantly increased the OFV by 109.012 units (p-value <0.01), [Table 21]. This reflected in CrCl explaining 27.72% of between subject variability in Cl. The exclusion of age as a covariate on Vc resulted in borderline significant increase in OFV by 6.7 units, but decision was made to include it in the final model as it resulted in explaining 23% of the estimated between subject variability in Vc.

Table 21

*Summary of univariate and multivariate covariate modeling steps*

Model number	Covariate relationship <sup>¥</sup>	MOFV	$\Delta$ MOFV <sup>Y</sup>
<b>Step 1: Univariate stepwise forward selection<sup>a</sup></b>			
0	CrCl on Cl	3146.729	-108.552
1	Age on Cl	3371.619	+116.4*
2	Age on Vc	3201.600	-53.681
3	LBW on Cl	3221.703	-33.578
4	TBW on Cl	3225.019	-30.262
5	BSA on Vc	3245.981	-9.300
6	TBW on Vc	3247.312	-7.696
<b>Step 2: Bivariate stepwise forward selection<sup>b</sup></b>			
6	CrCl on Cl and Age on Vc	3140.467	-6.262
7	CrCl on Cl and TBW on Vc	3142.924	+2.457*
8	CrCl and LBW on CL	3155.358	+14.891*
9	CrCl and TBW on CL	3219.894	+79.427*
10	CrCl on Cl and BSA on Vc	3443.772	+303.305*

Table 21

*Summary of univariate and multivariate covariate modeling steps (continued)*

Model number	Covariate relationship <sup>¥</sup>	MOFV	$\Delta$ MOFV <sup>Y</sup>
<b>Step 3: Stepwise backward elimination<sup>c</sup></b>			
11	Exclude Age	3146.512	+6.045**
12	Exclude CrCl	3249.479	+109.012
13	Exclude $\theta_2$ from Cl	3278.137	+137.85
14	Exclude $\theta_4$ from Vc	3211.434	+70.967

<sup>¥</sup>from multiple models per covariate-parameter relationship, the model with the least OFV included; MOFV: minimum objective function value; CrCl: Cockcroft-Gault equation creatinine clearance using lean body weight; Cl: vancomycin clearance; TBW: total body weight; LBW: lean body weight; Vc: vancomycin volume of distribution in central compartment; <sup>a</sup> compared to base model (OFV=3255.281); <sup>b</sup>compared with model 0; <sup>c</sup>compared with model 6; \* insignificant change in OFV; \*\*borderline significant change in MOFV.

#### 4.3.3 Final model

Vancomycin disposition best fitted a two-compartment model. The physiologic parameters, clearance (Cl) and central compartment volume of distribution ( $V_c$ ), were estimated with good precision [Cl: 5.23L/h, 95%CI: 4.72-5.74;  $V_c$ : 44L, 95% CI:37.7-50.3]. CrCl and age were significant covariates on Cl and  $V_c$ , respectively. The non-physiologic parameters,  $V_p$  and Q, were estimated to be 66.7L and 2.22 L/hr, respectively. Interindividual variability for Cl,  $V_c$ , and Q was 38.9%, 42.7%, and 97%, respectively. Table 22 summarizes the estimates of the final vancomycin population pharmacokinetic model.

Table 22

*Estimates of final vancomycin population pharmacokinetic model parameters*

Parameter	EBE <sup>¥</sup>	RSE <sup>€</sup> (%)	95% CI*
<b>Fixed parameter (Unit)</b>			
Cl (L/hr) = $\theta_1 * [(\text{CrCl (L/hr)}/7.11)]^{\theta_2}$			
$\theta_1$	5.23	5.01	4.72-5.74
$\theta_2$	0.827	13.5	0.607-1.05
Vc (L) = $\theta_3 * [(\text{AGE}/37)]^{\theta_4}$			
$\theta_3$	44	7.25	37.7-50.3
$\theta_4$	0.439	26.9	0.208-0.67
Vp (L) = $\theta_5$			
$\theta_5$	66.7	24.7	34.4-99
Q (L/hr) = $\theta_6$			
$\theta_6$	2.22	16.7	1.49-2.95
<b>Between subject variability (CV%)</b>			
$\omega_{\text{Cl}}$	38.99	17.8	31.44 - 45.28
$\omega_{\text{Vc}}$	42.78	80.3	32.40 - 68.63
$\omega_{\text{Vp}}$	-	-	-
$\omega_{\text{Q}}$	97.36	27.7	65.8 - 120.8

Table 22

*Estimates of final vancomycin population pharmacokinetic model parameters  
(continued)*

Parameter	EBE <sup>‡</sup>	RSE <sup>€</sup> (%)	95% CI*
-----------	------------------	----------------------	---------

**Residual unexplained variability (CV%)**

Proportional $\sigma$	21.47	15.6	17.88 - 24.54
-----------------------	-------	------	---------------

<sup>‡</sup> Post-hoc empirical Bayes estimates (EBE); <sup>€</sup> Relative standard error=(standard error /EBE) x100; \*95% confidence intervals; \*\*95% confidence intervals from 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the ranked bootstrap results ; **CV**: coefficient of variation; **Cl**: clearance of vancomycin; **V<sub>c</sub>**: volume distribution of vancomycin in the central compartment; **Q**: intercompartmental clearance of vancomycin; **V<sub>p</sub>**: volume of distribution of the peripheral compartment of vancomycin; **CrCl**: Cockcroft-Gault equation creatinine clearance using lean body weight;  $\omega$ : between subject variability related to PK parameter;  $\sigma$ : residual unexplained variability, including within-subject variability

#### 4.3.4 Final model evaluation

The final population PK model parameters for vancomycin are presented in [Table 22]. Fixed effects parameters were estimated with reasonable precision (RSE<30%) and lied within 95% CI of bootstrap analysis, showing model robustness [Table 23]. Goodness of fit plots show the observed concentrations randomly scattered near the line of identity of final model predicted concentrations, suggesting good fit of the final model [Figure 15]. Conditional weighted residual (CWRES) plots showed even distribution of population-predicted concentrations excluding the possibility of systematic bias and confirming the adequacy of the selected model. Eta-distribution plots of the final model showed approximate normal distribution, minimizing the possibility of underlying overlooked subpopulations or unexplored significant covariates [Figure 16]. Bootstrap mean and median estimates were close to the final model EBE, with 75.2% (376/500) of the 500 simulations showing successful convergence, indicating the robustness of the final model [Table 23].

Table 23

*Bootstrap analysis of final vancomycin population pharmacokinetic model*

Parameter	Final model			Bootstrap results		
	EBE <sup>¥</sup>	RSE <sup>€</sup> (%)	95% CI*	Mean estimate	Median estimate	95% CI**
<b>Fixed parameters (Unit)</b>						
CL (L/hr) = $\theta_1 * [(\text{CrCl (L/hr)/7.11})^{\theta_2}]$						
$\theta_1$	5.23	5.01	4.72-5.74	5.196	5.197	4.45-5.76
$\theta_2$	0.827	13.5	0.607-1.05	0.789	0.787	0.601-0.978
V <sub>c</sub> (L) = $\theta_3 * [(\text{AGE}/37)^{\theta_4}]$						
$\theta_3$	44	7.25	37.7-50.3	44.577	43.698	37.363-58.041
$\theta_4$	0.439	26.9	0.208-0.67	0.446	0.456	0.159-0.703
V <sub>p</sub> (L) = $\theta_5$						
$\theta_5$	66.7	24.7	34.4-99	76.23	60.568	37.87-274.819
Q (L/hr) = $\theta_6$						
$\theta_6$	2.22	16.7	1.49-2.95	2.397	2.298	1.537-4.065



Table 23

*Bootstrap analysis of final vancomycin population pharmacokinetic model (continued)*

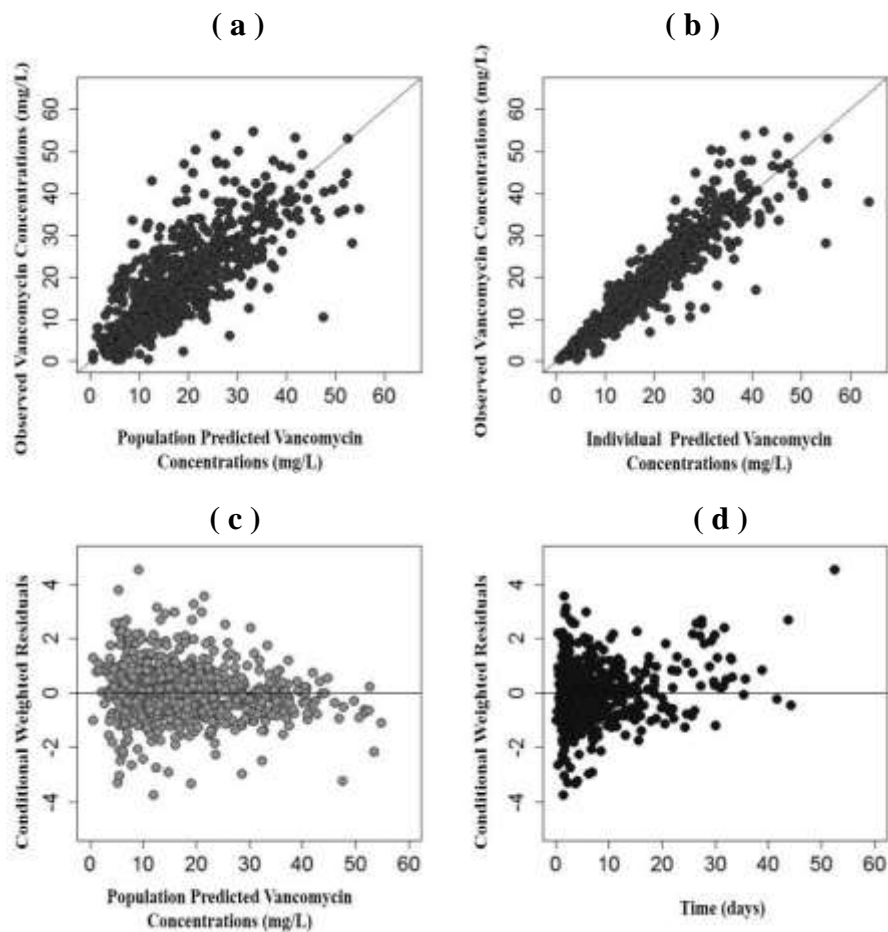
Parameter	Final model			Bootstrap results		
	EBE <sup>¥</sup>	RSE <sup>€</sup> (%)	95% CI*	Mean estimate	Median estimate	95% CI**
<b>Between subject variability (CV%)</b>						
$\omega_{Cl}$	38.99	17.8	31.44 - 45.28	39.69	39.11	32.28-47.09
$\omega_{Vc}$	42.78	80.3	32.40-68.63	51.64	44.00	6.05-91.99
$\omega_{Vp}$	-	-	-	-	-	-
$\omega_Q$	97.36	27.7	65.8 - 120.8	94.69	93.89	57.27-124.38

Table 23

*Bootstrap analysis of final vancomycin population pharmacokinetic model (continued)*

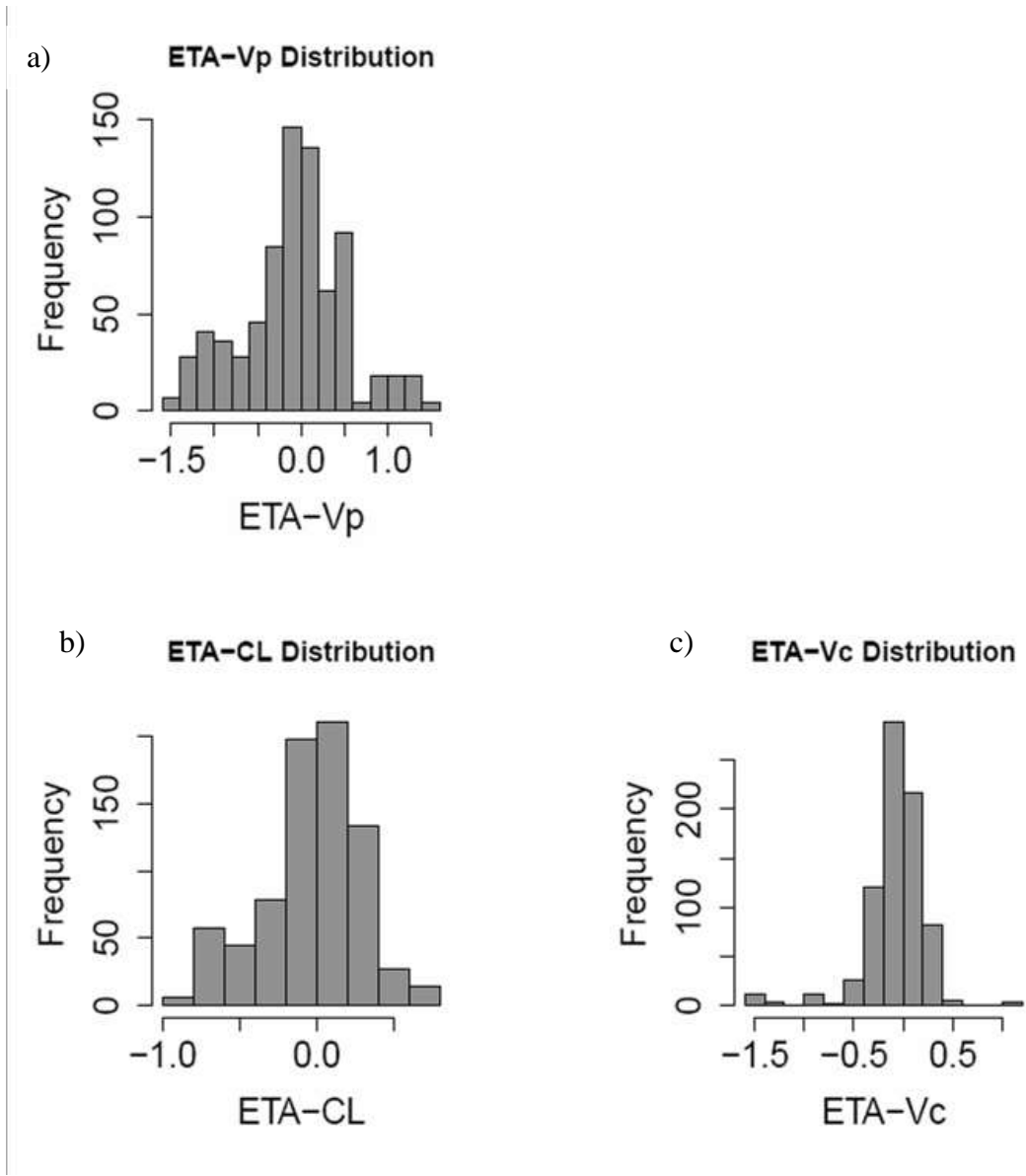
Parameter	Final model			Bootstrap results		
	EBE <sup>‡</sup>	RSE <sup>€</sup> (%)	95% CI*	Mean estimate	Median estimate	95% CI**
<b>Residual unexplained variability (CV%)</b>						
Proportional $\sigma$	21.47	15.6	17.88 - 24.54	20.91	20.85	17.69-24.44

<sup>‡</sup> Post-hoc empirical Bayes estimates (EBE); <sup>€</sup> Relative standard error= (standard error /EBE) x100; \*95% confidence intervals; \*\*95% confidence intervals from 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the ranked bootstrap results ; **CV**: coefficient of variation; **Cl**: clearance of vancomycin; **V<sub>c</sub>**: volume distribution of vancomycin in the central compartment; **Q**: intercompartmental clearance of vancomycin; **V<sub>p</sub>**: volume of distribution of the peripheral compartment of vancomycin; **CrCl**: Cockcroft-Gault equation creatinine clearance using lean body weight;  $\omega$ : between subject variability related to PK parameter;  $\sigma$ : residual unexplained variability, including within-subject variability



*Figure 15:* Goodness-of-fit plots of final vancomycin population pharmacokinetic model.

Observed vancomycin serum concentrations versus: a) final model population-predicted vancomycin serum concentrations; b) individual predicted vancomycin serum concentrations; conditional weighted residuals versus: c) final model population-predicted vancomycin serum concentrations; d) time



*Figure 16* : Eta distributions of final vancomycin population pharmacokinetic model  
 Legend: Eta distributions of final vancomycin population pharmacokinetic model versus: a) volume of distribution of vancomycin in the peripheral compartment (Vp); b) clearance of vancomycin (Cl); c) volume distribution of vancomycin in the central compartment (Vc)

*4.3.5 Assessing the need for vancomycin dosing nomograms specific to the population in Qatar.*

Table 24 summarizes vancomycin population parameter estimates reported in other adult non-dialysis populations in which vancomycin exhibited two-compartment model disposition. Weight, age, CrCl and clinical statuses were similar to the present cohort [Table 24]. The physiologic population parameter estimates were comparable to the present findings, and ranged between 0.2-1.1 L/kg and 0.05-0.08 L/kg/hr for Vc and Cl, respectively. Based on that, we conclude that no specific vancomycin dosing nomograms are required in the local population.

Table 24

*Vancomycin population pharmacokinetic parameters from selected studies\**

Author, Publication year	Data nature	Country, n	Disease /Clinical setting	CrCl (L/hr)	Age in years	Weight (Kg)	Clv (L/hr/Kg)	V <sub>d</sub> (L/Kg)	Variability %CV
Yashuara M et al, 1997(165)	Sparse data collected during routine TDM between August 1993 and March 1995	Japan; 1253 VBS collected from 190 patients	MRSA hospitalized patients across 19 hospitals	4.626±3.054 [0.411-.] a	64.3±13.8 [19.3-89.6]	52.3±9.6 [25.5-75]	0.07	1.11	ωCL=38.5(30.6-45) ωV=25.4(19.7-30) σ=23.7(21.4-25.8)

Table 24

*Vancomycin population pharmacokinetic parameters from selected studies\*(continued)*

Author, Publication year	Data nature	Country, n	Disease /Clinical setting	CrCl (L/hr)	Age in years	Weight (Kg)	Cl <sub>v</sub> (L/hr/Kg )	V <sub>d</sub> (L/Kg)	Variability %CV
Llopis-Saliva et al, 2006 ( <a href="#">96</a> )	Retrospective sparse data from routine TDM collected over 48 months	Spain; 357 VBS collected from 50 patients	ICU admitted subjects suspected (66%) or confirmed (34%) vancomycin susceptible infection	0.457±2.057 [0.98-7.2]a	60 (17) [18-81]b	60.6±15.55 [40-130]	0.056	0.41	ωCL=29.2(12. 93-45.47) ωV =36.4(19.8- 53.6) σ=42.4% (13.23-68.56)

Table 24

*Vancomycin population pharmacokinetic parameters from selected studies\*(continued)*

Author, Publication year	Data nature	Country, n	Disease /Clinical setting	CrCl (L/hr)	Age in years	Weight (Kg)	Clv (L/hr/Kg)	V <sub>d</sub> (L/Kg)	Variability %CV
Dolton et al, 2010 ( <a href="#">166</a> )	Routine TDM data collected retrospectively between 2000 and 2006 (cases) and prospectively between Jul. 2007 and Oct. 2007 (controls)	Australia; 70 patients suspected & confirmed infection; cases (n=37), controls (n=33)	<b>Cases:</b> Severely burned ; burns unit <b>Controls:</b> Patients without burns	Cases <sup>a</sup> : 7.464±3.33 Controls <sup>a</sup> : 4.5±2.87	Cases <sup>d</sup> : 34(15-88) Controls <sup>d</sup> : 72(38-95)	Cases d: 69(42.5-116) Controls d: 67 (48.9-111)	Cases: 0.086 Controls : 0.051	Cases: 0.880 Controls: 0.978	ωCL=32.7% ωV =19.1% IOV- CL=11.7% IOV-V=23.5 σ1 =29.3% σ2 =0.229 mg/L



Table 24

*Vancomycin population pharmacokinetic parameters from selected studies\*(continued)*

Author, Publication year	Data nature	Country, n	Disease /Clinical setting	CrCl (L/hr)	Age in years	Weight (Kg)	Clv (L/hr/Kg)	V <sub>d</sub> (L/Kg)	Variability %CV
Yamamoto et al, 2009 ( <a href="#">167</a> )	Retrospective routine TDM cases documented between Jan. 2004 to Nov. 2005	Japan; 106 subjects with 356 VBS	Patients (n=100,311 VBS): suspected or confirmed gram positive infection. Healthy volunteers: (n=6 males) 45 VBS	Patients a: 4.76 ±2.5 [0.918-13.13] Healthy volunteers a: 5.36±0.624 [4.6-6.36]	Patients a: 65.4±15.1 [25.8-99.7] Healthy volunteers a: 21.7±2 [20-25]	Patients a: 52.6±12.7 [28.7-97] Healthy volunteers a: 60.3±3.7 [55.7-64.2]	Patients: 0.0548 rs: 0.065	Patients: 0.478 s: 0.205	ωCL=37.5% ωV =18.2% σ=14.3%

\*In alignment with our population, the selected studies report two-compartment vancomycin pharmacokinetic models in adults who were not on dialysis; only clinically relevant parameters are reported; **a**: mean $\pm$ SD [range]; **b**: median(IQR), **c**: mean (95%CI), **d**: median(range); **VBS**: vancomycin blood samples; **CV**: coefficient of variation;  $\omega$ : intraindividual variability;  $\sigma$ : residual unexplained variability

## CHAPTER 5: DISCUSSION, FUTURE STUDIES AND CONCLUSIONS

### 5.1 : Phase I: Multicenter retrospective evaluation of vancomycin TDM service appropriateness

The findings of this multicenter evaluation suggest that the local vancomycin TDM practices varied from evidence-based clinical practice guidelines recommendations, and do not usually align with basic clinical pharmacokinetic principles. Per the vancomycin TDM appropriateness evaluation tool, the vast majority (90.4%, n=188) of the vancomycin TDM cases were conducted inappropriately. The main pre-analytical indices that were incorrect at many instances were the sampling time and the labeling of vancomycin blood specimens. The importance of these two main pre-analytical factors cannot be overemphasized, as they account for substantial rates of erroneous post-analytical actions and cost-avoidance areas(43, 168); clinicians often adjusted doses based on incorrectly timed blood samples. Vancomycin TDM concentrations that were drawn earlier had been reported to have higher rates of falsely elevated vancomycin serum concentrations compared to those drawn at appropriate times, which significantly impacted the type of post-analytical action taken (103). Early sampled specimens had twice the likelihood to be supratherapeutic and half the likelihood to be subtherapeutic, resulting in statistically significantly higher rates of vancomycin treatment discontinuation, underdosing, or re-ordering TDM levels compared to correctly timed specimens (103). Due to the high rates of inappropriately timed vancomycin blood specimens, the appropriate post-analytical action was to re-order the vancomycin blood concentration, presenting significant avoidable economic burden on the healthcare system.

However, the interpretation of vancomycin blood concentrations seldom showed the consideration of the timing of the specimen, signifying potential inappropriateness area of post-analytical actions. Another area of post-analytical action that needs to be improved is the dose-adjustment practices. The reasons for these findings can be attributed to the fact that to date, no specialized clinical pharmacokinetic TDM service exists in secondary and tertiary healthcare settings in Qatar, where pharmacists seldom provide TDM services. Nurses education regarding the importance of accurate timing of TDM specimens is warranted. Another potential reason may be the poor documentation practices of TDM service indices highlighted in this study.

To our knowledge, the present evaluation is the first that explores the impact of vancomycin TDM service quality on the clinical outcomes of vancomycin treatment. Our findings of relatively high morbidity, hospitalization days and mortality with vancomycin treatment have been significantly associated with inappropriate vancomycin TDM service practices. The relatively long hospitalizations and high rates of treatment failures present sources of avoidable economic burden on the healthcare system and the society. The philosophy of pharmaceutical care is the essence of any clinical pharmacy service, which is to maximize the clinical, economic and humanistic outcomes of pharmacotherapy (81). Per the present results, the local vancomycin TDM service fails to achieve the goals of pharmaceutical care, warranting significant revision and improvement.

Our findings are consistent with the few vancomycin-specific studies that explored the appropriateness of vancomycin TDM practices in the MENA region (43, 107, 110), and elsewhere (44, 103, 106). Al-Zaabi and

colleagues reported two studies in Oman that were conducted across different time points ([43](#), [110](#)). Most of the inappropriately timed vancomycin TDM requests were appropriately indicated ([43](#)). Moreover, dose adjustments were commenced in many incorrectly sampled specimens, signifying false dosing and inappropriate interpretation of TDM results ([43](#)). Consistent to our findings, higher tendency to applying dose adjustments in response to toxic concentrations more than subtherapeutic concentrations had been reported ([110](#)). Yet, the clinical impact of such practices were not assessed in the previous studies, and documentation quality was not reported ([43](#), [110](#)). Dose adjustment practices were insufficient in an Iranian hospital, and were not based on vancomycin serum concentrations, which may explain the relatively high rates of nephrotoxicity and supratherapeutic vancomycin serum concentrations reported in their setting ([107](#)). Despite the fact that higher rates of appropriate glycopeptide TDM practices have been observed in well-developed settings ([44](#), [103](#), [106](#)), the quality of dose adjustments ([44](#), [106](#)) and sampling time remains suboptimal in the West ([44](#), [103](#)). Unlike the present work, not all studies applied triangulation, pretesting, pilot-testing techniques or explored the clinical impact of inappropriate application of vancomycin TDM.

The results from this multicenter evaluation are of local, regional and global value. The identification of the deficient areas of local routine vancomycin TDM practices serves as an invaluable tool in guiding policymakers, health administrators, and practitioners to devise ways of optimizing vancomycin TDM services utilization, minimizing costs, and improving health outcomes in the local setting. In Qatar, most of the

clinicians are expatriates originating from the MENA region, suggesting that similar practices may be observed in unexplored clinical settings where vancomycin is used in the region. Thus, our findings will contribute to improved healthcare system efficiency and quality indicators such as decreased personnel time utilization and the minimization of wastage of analytical resources in the MENA region. Moreover, this evaluation serves as a revelation to the potentially limited clinical pharmacokinetics skills and knowledge of healthcare professionals graduating from MENA-based pharmacy curricula, suggesting the need for curricula revisions and improvements. Thirdly, the present evaluation is the first that suggests vancomycin TDM service inappropriateness as an unexplored source of suboptimal clinical outcomes of vancomycin treatment. This suggests potential global significance. The reported high rate of clinical failures associated with the assessed vancomycin TDM cases suggests vancomycin TDM service inappropriateness as a possible source of emergence of vancomycin resistant bacterial strains reported worldwide.

The present study has several strengths, suggesting high internal and external validity of its findings. To the best of our knowledge, this is the first multi-center vancomycin TDM service-specific evaluation in the MENA region. Also, this is the first study that relates vancomycin TDM service appropriateness indices to clinical safety and efficacy outcomes in adult non-dialysis patients, which adds a global value and impact of its findings. The applied methodology was robustly designed to minimize bias. The application of global sampling, pre-testing and pilot testing the data collection forms, double data collection per TDM case, pre-testing and pilot-

testing of vancomycin TDM appropriateness evaluation tool, and triangulation suggest high internal validity of this work. Definitions of clinical outcomes was based on studies reporting clinical outcomes of vancomycin treatment, to ensure comparability with the published literature. Moreover, the assessed cohort is representative of secondary and tertiary healthcare settings, and a wide range of infections that require vancomycin treatment. Therefore, the highlighted practice deficiency areas that need to be acted upon are of considerable generalizability and external validity in clinical situations when IV vancomycin is indicated in adult non-dialysis patients.

Yet, this study has several limitations, providing basis for further future research studies. The appropriateness of vancomycin treatment indication (i.e. initiation, continuation or discontinuation) was not assessed. This study did not include pediatrics or dialysis population or long-term care facilities. The sample size was relatively small due to the limitation of cases to those documented in the EMR as retrieving paper-documented vancomycin TDM records was not feasible. We could not identify the provider of the TDM service from the EMR and thus the impact of pharmacist-provided versus physician-provided vancomycin TDM service appropriateness could not be assessed. An important component of TDM evaluation is the biochemistry analytical aspect that was beyond the scope of the current evaluation. In addition, the impact of inappropriate TDM practices on the MIC creep in the local setting was not explored across the duration of the included TDM cases. Studies investigating the impact of inappropriate vancomycin TDM practices on the global and regional and

local MIC creep will be of valuable addition to the current body of literature. The cost-effectiveness and cost-avoidance, quality of life of routine vancomycin TDM service in relation to the explored appropriateness indices were not explored. Future studies aiming to explore these economic and humanistic outcomes of routine vancomycin TDM services are warranted.

In conclusion, high discrepancy remains between evidence-based vancomycin TDM recommendations and routine pragmatic application in Qatar, contributing to clinical failures, longer duration of hospitalization and potential sources of avoidable costs. High rates of inappropriately timed samples, erroneous post-analytical actions, and poor documentation and labeling qualities were identified in this study. Efforts should be geared towards exploring setting-specific reasons for deficient TDM practices and strategies for vancomycin TDM quality improvement.



## 5.2 Phase II: Clinical and Pharmacokinetic Outcomes of the traditional peak-trough-based versus the trough- based vancomycin TDM approaches: A randomized controlled trial

To our knowledge, the present study is the first pragmatic head-to-head RCT that prospectively compared two routinely used vancomycin TDM approaches; peak-trough versus the 2009 IDSA-ASHP recommended trough-only vancomycin TDM approaches. Studies have suggested that vancomycin TDM was associated with higher clinical success rates and less nephrotoxicity compared to non-TDM groups (39, 60). To date, studies in this area compared vancomycin TDM recipients with non-TDM recipients (39). The meta-analysis of Ye ZK and colleagues showed that most studies were of observational design, with only one RCT (39). Therefore, there is paucity of evidence about which TDM approach translates into better clinical outcomes in routine setting. The present pragmatic RCT aimed to address this question. Specifically, this study aimed to compare the clinical and pharmacokinetic outcomes associated with these peak-trough-based versus trough-only-based vancomycin TDM approaches, as well as to explore the association between vancomycin 24hr AUC/MIC and clinical success.

In the present study, peak-trough-based vancomycin TDM was significantly associated with higher infection cure rates compared to trough-only-based vancomycin TDM. Interestingly, trough-based vancomycin dosing was associated with higher failure rates. This can be attributed to the finding that peak-trough-based vancomycin dosing approach resulted in higher rates of target troughs and peaks compared to trough-only-based

vancomycin dosing approach. Therefore, peak-trough-based TDM recipients required less dose adjustments to achieve pre-determined target concentrations. Although not statistically significant, peak-trough-based vancomycin TDM recipients required shorter durations of vancomycin treatment and LOS. Compared to the 2009 IDSA-ASHP recommended approach (i.e. the trough-based vancomycin TDM), the peak-trough-based vancomycin TDM recipients required less average vancomycin single doses and total daily doses by 370 mg/dose and 927 mg/day. More importantly, the trough-based vancomycin TDM recipients received significantly higher cumulative vancomycin doses by 6.3 grams.

To determine the 24-hr AUC that was best associated with therapeutic cure in the present cohort, CART modeling was conducted. Upon univariate analysis, CART identified a 24-hr AUC of  $\leq 863.97$  mg.hr/L to best correlate with therapeutic success. Upon multivariate analysis, CART identified CrCl, 24-hr AUC, and the type of vancomycin TDM approach as significant determinants of therapeutic outcomes with 100%, 58.4%, and 45.8% normalized importance to the model, respectively.  $\text{CrCl} < 7.85$  L/hr was highest correlated with cure rates [76.1%, n=35], followed by a 24-hr  $\text{AUC} \leq 1255.98$  mg.hr/L [86.1%, n=31]. All patients who achieved 24-hr  $\text{AUC} \leq 1255.98$  mg.hr/L and received peak-trough-based vancomycin dosing achieved clinical success. In contrast, maintenance of 24-hr  $\text{AUC} > 564.117$  mg.hr/L was required to achieve cure in trough-only-based TDM recipients. Duration on vancomycin treatment before TDM, infected physiologic compartment, and ethnicity were not found to correlate with cure in CART. High predictive performance of the model was observed; the model correctly

predicted therapeutic outcomes in 86.2% (empiric and definitive cases) and 100% (definitive cases only) of the times; respectively.

The findings of this study complement the reported 24-hr AUC/MIC targets with vancomycin treatment by: 1) confirming the literature reported minimum targets; 2) suggesting a maximum target that if exceeded, no extra clinical benefit will be observed. Assuming a MIC of 1mg/mL, the present work reports 24-hr AUC/MIC > 564.117 hours as the minimum breakpoint for cure while being dosed and monitored using the trough-only TDM approach. This breakpoint is higher than the minimum AUC/MIC cure breakpoints that ranged between 398-451 hours in seven observational cohort studies that used broth microdilution technique (169). Unexpectedly, a minimum AUC/MIC breakpoint was only needed when trough-only-based vancomycin dosing was applied, while peak-trough-based vancomycin dosing was not associated with a minimum threshold. These findings can be explained by the results of the largest most recent prospective study by Neely and colleagues who compared AUCs obtained from trough-only ( $AUC_T$ ) and peak-trough-only ( $AUC_{PT}$ ) models to the AUC obtained from the full model ( $AUC_F$ ) (48). The full model was built from an independent data set that consisted of richly sampled concentrations in addition to the peaks and troughs. The  $AUC_{PT}$  more precisely and accurately estimated the  $AUC_F$  with less variability ( $R^2=0.94$ ) compared to the  $AUC_T$  ( $R^2=0.7$ ). Neely's group reported that the AUCs calculated from peak-trough model showed better estimates; the median  $AUC_F$  was more than  $AUC_{PT}$  by 159.3 mg.L/hr [95% CI: 63.6-284.6; *p*-value <0.001]; median  $AUC_F$  was more than  $AUC_T$  by 341.9 [95% CI: 189.8-553.4; *p*-value <0.001]. Thus, this study suggests that peak-trough-

based vancomycin dosing is associated with achieving the minimum AUC/MIC threshold for cure at most times, while trough-only-based monitoring has lower probability to achieve the minimum AUC/MIC targets.

In addition, the present work identified a maximum 24-hr AUC/MIC threshold of 1255.98 hours, that if exceeded, no extra clinical benefit is likely. It has been reported that targeting, higher 24-hr-AUC/MIC ratios was associated with better clinical outcomes ([169](#), [170](#)). Men and colleagues reported a systematic review of nine observational cohort studies, proving that higher AUC/MIC ratios were associated with significantly less rates of infection treatment failure and mortality by 53% and 61%, respectively ([169](#)). Patients with MRSA bacteremia who achieved higher 24hr AUC/MIC ratios had significantly higher cure rates, less bacterial persistence and lower mortality rates ([170](#)). Yet, the question remained in the literature regarding the maximum AUC/MIC threshold that should not be exceeded to prevent vancomycin-related ADRs. Hence, the present work succeeded in identifying a maximum AUC/MIC threshold to achieve clinical benefits without compromising patient safety.

Emerging evidence suggests the limited and questionable clinical benefit of the 2009 IDSA-ASHP recommended trough-only-based vancomycin dosing in complicated infections ([170-172](#)). According to a meta-analysis of 17 observational studies, vancomycin trough-only-based dosing that targeted higher troughs >15mg/L was associated with significantly more nephrotoxicity and no significant improvement in mortality or cure rates ([171](#)). Similar findings were reported in deep-seated MRSA vancomycin-treated patients, as troughs >15mg/L did not result in

shorter LOS, less mortality rates or higher treatment success rates compared to troughs <15mg/L (172). In fact, vancomycin trough >15mg/L was associated with higher nephrotoxicity incidence (172). A meta-analysis of 14 observational cohort studies, with a total of 1677 participants showed that vancomycin dosing based on 2009 IDSA-ASHP trough targets (15-20mg/L) was not associated with better clinical outcomes in relation to death, persistence of bacteremia and treatment failure in patients with *S.aureus* bacteremia (170). Vancomycin trough concentration is a single point estimate that does not optimally explain more than half the BSV in AUC and is associated with a wider range of AUCs that is hard to correlate with safety and effectiveness outcomes (54). The findings of this RCT concur with the emerging evidence of limited clinical utility of trough-only directed vancomycin dosing, demanding other vancomycin dosing methods that would result in attainment of AUC/MIC targets. Peak-trough-based vancomycin dosing seems a promising approach that correlates better with AUC/MIC targets, which has strong evidence of clinical benefit.

This RCT suggests that peak-trough-based vancomycin dosing is associated with lower vancomycin exposure duration, cumulative doses, as well as less hospitalization days. Similar clinical benefits of vancomycin peak concentration monitoring have been suggested by other studies (60, 99, 117). In a prospective observational study, pharmacokinetic-based vancomycin TDM group received mean lower vancomycin dosages by 5 grams, and required shorter treatment duration and LOS by 2 and 6.5 days, respectively (60). A recent finding by Hong and colleagues reported that peak-trough-based vancomycin TDM allowed significantly better attainment

of therapeutic vancomycin concentrations (117). These findings are of clinical and economic relevance. It has been reported that vancomycin-related ADRs such as nephrotoxicity and neutropenia may be exposure-related (54, 119, 129, 140, 141, 173-175). For example, vancomycin daily doses that exceeded 4 grams were associated with nephrotoxicity (173), with trough concentrations exceeding 15 mg/L with significantly higher risk (119). Therefore, peak-trough-based vancomycin dosing provides a potential strategy to decrease vancomycin exposure, which will reflect into lower medication utilization, lower rates of emergence of vancomycin resistant strains of bacteria, and lower risk of vancomycin-related ADRs. Furthermore, the lower hospitalization days with peak-trough-based vancomycin dosing would potentially result in lower incidences of nosocomial infections. Thus, this approach provides a potential strategy to maximize clinical outcomes with vancomycin treatment, as well as decrease the economic burden on healthcare systems due to complicated gram-positive infections.

Antibiotic stewardship programs (ASP) are evidence-based efforts by healthcare systems to optimize the utilization of antibiotics, aiming to decrease antimicrobial resistance, improve patient outcomes and assure cost-effective therapy (176). Optimization of dosing and duration of antimicrobial use is one of the strategies targeted by ASP to decrease antibiotic consumption, while assuring cost-effective therapy (176, 177). The rising antibiotic consumption represents a challenge for ASPs. For example, estimates of more than 3 million kilograms of antibiotic consumption has been reported in US alone during 2009 (176). Empiric antimicrobial treatment in the setting of critical illness contributes to the challenge of rising

antibiotic consumption. This is confirmed by the present study in which vancomycin was empirically administered in approximately half the study participants (n=30, 46.7%); approximately half of the study participants were critically-ill and required hospitalization in critical care units. It has been reported that in critical illness, vancomycin treatment indications are empiric, with approximately quarter of episodes initiated as definitive treatment ([177](#), [178](#)). From 312 subjects in trauma and surgical intensive care ward who were initiated on empiric antimicrobial therapy, only 25.6% were found to have an infection ([179](#)). In a multicenter prospective cohort study involving 8 medical and surgical intensive care units in North American/European setting, empirical antimicrobial therapy was initiated four times more than the rate of confirmed infection ([180](#)). More than half of the cases receiving empiric therapy continued antibiotic treatment for more than 4 days ([180](#)). Antimicrobial treatment in medical intensive care unit was used as empiric therapy in 94% of the cases in Qatar ([181](#)). Mean empiric antibiotic use has been reported to be 3 days and ranged from 1 to 20 days ([179](#)). Evidence suggests the cost-effectiveness of vancomycin TDM in some patient groups, such as those receiving concomitant nephrotoxins or who are critically-ill such that hospitalization in intensive care units was required ([182](#)). The limited cost-effectiveness in all clinical situations may be attributed to the method of TDM approach applied. Hence, peak-trough-based vancomycin TDM maybe a potential cost-effective strategy, warranting further research. According to the current findings, peak-trough-based vancomycin dosing provides a promising approach to achieving the goals of ASPs. This study

suggests antimicrobial consumption as a measure to benchmark antimicrobial TDM approaches.

This study has several strengths. First, the present RCT is of pragmatic nature, aiming to test the effectiveness of therapy compared to another comparator that is routinely used in clinical settings (trough-only-based vancomycin TDM). The key feature of pragmatic designs is the ability to assess the effectiveness of an intervention in routine situations to maximize the external validity of the study findings (183). Due to the limited generalizability of exploratory RCTs to routine clinical practice, the concept of pragmatism has emerged during the past decades (183-185). Exploratory RCT are conducted under ideal circumstances under which an intervention is more likely to work which is not how real-life situations are in clinical settings; thus, they possess limited generalizability and may fail in many routine clinical situations (183). Therefore, it has been reported that the plethora of exploratory RCTs are of limited utility to healthcare policymakers and clinicians (185). Due to the pragmatic nature of this study, the researchers did not intervene on vancomycin's indication appropriateness and initial dosing; suspected or confirmed complicated gram-positive infections requiring vancomycin treatment were included, with no restrictions to MRSA like other AUC studies. The study setting included multiple centers and wards to be reflective of the variabilities in clinician practices. In addition, no restrictions on infection type, critical illness state, pharmacotherapeutic or mechanical co-interventions were applied, to assure representativeness of routine clinical situations. Thus, the implications of the study findings are of clinical relevance, as it tested effectiveness rather than efficacy alone.



Second, the prospective nature of the study allowed accurate vancomycin dosing and blood specimen collection. The accuracy of sampling times and dosing is crucial aspect towards the assurance of the internal validity of clinical pharmacokinetic studies. Unlike most clinical evaluations that estimated the AUC based on estimated renal clearance (i.e. Cockcroft-Gault equation) which does not accurately predict vancomycin Cl ([54](#)), the present work used actual individualized vancomycin clearance to estimate the AUC. Together, these aspects suggest high internal validity of the study, with considerable generalizability.

The findings of the current study need to be interpreted with caution due to some important limitations. First, the limited sample size and unblinded nature of this study warrant future larger scale studies to confirm the reported findings. The limited sample size was due to the slow recruitment rate. Second, the exact MIC of confirmed gram-positive cultures were not available for all patients since many received vancomycin as empiric treatment. For patients with confirmed cultures sensitive to vancomycin, HMC laboratories reported to have MIC of 1mg/mL at all instances with values less than 1 mg/mL rounded to 1mg/mL. Finally, the appropriateness of vancomycin initiation was not assessed in the present work. Thus, the findings of this RCT need to be interpreted considering these limitations. Future larger scale double-blinded pragmatic RCTs are needed to confirm the findings of this work. Also, this study serves as a foundation to future cost-effective analyses that will be invaluable for clinicians and clinical practice guideline developers.

In conclusion, this is the first pragmatic RCT that compared peak- trough-based versus trough-only-based vancomycin TDM approaches. Compared to the IDSA-ASHP recommended trough-based vancomycin TDM strategy, the traditional peak-trough-based vancomycin TDM strategy was associated with higher cure rates, less vancomycin utilization, less requirement for dose adjustments to achieve therapeutic concentrations, and shorter duration of hospitalization. Future larger scale double-blinded trials are warranted to confirm these study findings.

### 5.3 Phase III: Vancomycin population pharmacokinetics

Vancomycin is one of the few alternatives available for the treatment of serious methicillin-resistant gram-positive infections. In clinical settings, vancomycin dosing nomograms derived from population-specific pharmacokinetic parameters are used to guide vancomycin dosing with expected good predictive performance (97). However, the vancomycin dosing nomograms applied locally have been established based on published Western vancomycin population pharmacokinetic models, which may vary from the MENA population parameters. The implementation of vancomycin dosing nomograms derived from Western population to MENA population may result in suboptimal outcomes with vancomycin treatment due to its exposure-dependent clinical effectiveness properties (169). To the best of our knowledge, the present study is the first that explores vancomycin population pharmacokinetics and the effect of patient-specific covariates in the Middle Eastern population, aiming to explore the need for MENA-population specific vancomycin dosing nomograms.

The clinical pharmacokinetics of vancomycin in adult non-dialysis MENA population were quantified using nonlinear mixed effects modeling (NLMEM) approach. Vancomycin disposition best fitted a two-compartment model as reported in previous studies (154, 167, 186, 187). PK parameter estimates from the base model showed acceptable precision (RSE<30%), but relatively high between subject variability ( $\omega_{Cl}$ = 66.71%,  $\omega_{vc}$ =66.56%). Upon covariates modeling, age and CrCl were the only significantly influential covariates in the final model. CrCl was the only identified significant covariate on vancomycin Cl, as it explained 27.72% of between subject

variability in vancomycin Cl. Age was the only significant covariate on  $V_c$ , as it accounted for 23% of the estimated between subject variability in  $V_c$ . This resulted in improving the precision of the clinically relevant physiologic parameters, Cl and  $V_c$ . [CL:5.23L/h, (0.075 L/hr/Kg), 95%CI: 4.72-5.74 L/h;  $V_c$ : 44L (0.63 L/Kg), 95%CI: 37.7-50.3 L ].

Overall, the findings of this analysis are similar with other reported two-compartment vancomycin models in adult non-dialysis patients. According to the review conducted by Marsot et al, two-compartment models best described vancomycin population PK in adults in six studies ([154](#)). According to those studies, median (range) fixed effects population estimates of Cl and  $V_d$  in adults was 0.051 (0.031–0.086) L/h/kg, and 0.864 (0.388–2.040) L/kg, respectively. Similar to our findings, none of the explored categorical covariates, such as gender, significantly affected vancomycin pharmacokinetic parameters ([154](#)). Studies reported that creatinine clearance and age explained 20-30% and 10% of between-subject variability in vancomycin clearance, respectively ([154](#)).

Consistent with the trends observed in the covariate plots of the present analysis, several studies included weight as a significant covariate on  $V_c$  or Cl in final population vancomycin model ([96](#), [154](#), [167](#), [188](#)). Despite that, forward selection-backward elimination procedures of the present work did not detect weight as a significant covariate on either vancomycin Cl or  $V_c$ . Similarly, Purwonugroho et al. reported a two-compartment model in adult Thai population, with CrCl and age as the only significant covariates on vancomycin Cl and  $V_c$  ([187](#)). Indeed, CrCl accounts for weight and age in its equation, which may explain these findings. Moreover, the age accounts for

changes in body compartments compositions (i.e. muscle mass, fat mass, body water composition, etc). Therefore, age can be considered inclusive of body weight as a covariate in explaining between-subject variability in Vc. These findings suggest the inclusion of weight in addition to age or CrCl adds unnecessary redundancy to the final population model.

Despite the inclusion of age and CrCl as significant covariates in the present final population pharmacokinetic model, interindividual variabilities for Cl and Vc remained to be 38.9% and 42.7%, respectively. This is consistent with the results of other vancomycin population pharmacokinetic models in adults ([96](#), [154](#), [167](#), [188](#)). In an Asian population, between subject variability for Cl and Vc, was reported to be 35.78 and 20.93%, respectively ([187](#)). Marsot's review reported vancomycin clearance interindividual variabilities to range from 19.8–38.5%, with an average of 30% ([154](#)). Interindividual variability in Vc ranged from 18.2–48.0% with an average of 30% ([154](#)). The similarities in the reported between subject variabilities in Cl and Vc across the reported studies and the present work, suggest the presence of other significant covariates that were not detected in the present analysis. Together with the present results, these findings indicate that ethnicity does not significantly influence vancomycin clinical pharmacokinetics. However, this cannot be confirmed based on the present cohort due to the large heterogeneity of the cohort regarding ethnicity. Thus, future studies with strict ethnicity-based inclusion criteria with subpopulation stratification are warranted.

Vancomycin disposition has been found to be affected by individual factors such as illness status, infection type, renal function and age ([154](#), [167](#),

[187](#)). Thus, vancomycin pharmacokinetics show clinically significant inter-individual variabilities, warranting individualized dosing ([32](#)). Indeed, the heterogeneity of clinical disease states in the present cohort may partly account for the remaining between-subject variabilities in vancomycin Cl and volume of distribution in the final population model. In this analysis, infection type/infected physiologic compartment did not significantly influence vancomycin PK parameters. This can be attributed to the heterogeneity of the studied cohort, as it included 11 types of infections. The reclassification into four physiologic compartments did not detect any relationships as well, possibly due to the limited sample size of the infected compartment subgroups. In support of this explanation, several studies reported disease-specific changes in hemodynamic and cardiovascular factors (other than CrCl and age) that influenced renal clearance ([189-193](#)). Therefore, vancomycin future population pharmacokinetic studies strictly exploring larger infection-homogenous subgroups are required.

Emerging studies elucidate that renal drug clearance is influenced significantly by disease states and not only CrCl ([189-193](#)). Augmented renal clearance (>150mL/min) was detected despite normal serum creatine concentrations, with increased cardiac output and plasma atrial natriuretic peptide concentrations in traumatic brain injury patients ([189](#)). A multicenter prospective cohort confirmed these findings as augmented renal clearance (130 mL/min/1.73m<sup>2</sup>) was detected despite normal plasma creatinine concentrations in patients across four ICUs in 4 different countries ([190](#)). Trauma patients versus septic patients exhibited higher prevalence of augmented renal clearance ([191](#)). Cardiac index weakly correlated with CrCl

in septic patients ( $r = 0.508$ ,  $P = 0.001$ ), but did not exhibit correlation in trauma patients [ $r = -0.012$ ,  $P = 0.951$ ] ([191](#)). Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were associated with augmented renal clearance. Moreover, multivariate analysis identified modified sequential organ failure assessment (SOFA) scores less than  $\leq 4$  as significant risk factors for accelerated renal clearance ([191](#)). These clinical diagnostic tools were not explored in the present analysis as well as previous population pharmacokinetic studies. Moreover, the effects of other pharmacotherapeutic interventions on renal drug clearance should be taken into account. For example, a systematic review reported that carperitide and nesiritide increased urine output and CrCl in cardiovascular surgical patients ([192](#)). Vancomycin clearance is affected partly by tubular secretion. Hence, studies on renal transporters and co-medications received in different disease states (e.g. diuretics) can further explain the still reported between subject variabilities in vancomycin clearance, despite accounting for age, weight and creatinine clearance ([193](#)). These factors are still not explored in vancomycin PK studies, warranting further research.

Similar to the findings of this analysis (21.5%), residual unexplained variability (RUV) was estimated to approximate 20% in previous vancomycin population PK analyses ([154](#)). Remaining RUV can be due to variabilities as well as errors in vancomycin analytical methods. The inclusion of data from different study sites, study designs (prospective versus retrospective) and time points did not result in higher residual variability than other studies. Interestingly, despite the considerable number of imputed CrCl records, the RUV was not higher than previous reports. The combination of

routine sparse sampling (retrospective) and dense-sampling (prospective), vancomycin concentration-time profiles did not increase the residual variability compared to other models. These findings imply that the imputation techniques applied in this study, as well as routine TDM monitoring data can be used to precisely and accurately estimate population pharmacokinetics.

The present analysis confirms the results of the numerous vancomycin population PK models that have been reported in adult non-dialysis patients ([154](#)), and suggests that MENA-population-specific vancomycin dosing nomograms may not be required. The results of the present PK analysis can be used in therapeutic drug monitoring in the MENA population. However, similarities between the covariates of the studied population and the respective patient case should be considered. For example, the present study did not accommodate for morbidly obese individuals or ascites patients. The clinical utility of vancomycin population pharmacokinetic models depends on the covariate distribution similarity between the model development population and the patient population to which the model will be applied. For example, Deng's group explored the predictive performance of 10 published vancomycin pharmacokinetic models in their Chinese population ([194](#)). The similarity in covariate distribution between the model development dataset and model validation dataset significantly impacted the predictive performance in their population; with the model developed from a population with similar covariate distribution to their population ([187](#)).



The present analysis has several strengths. Several measures were applied to assure the reliability of the datasets. Data collection was conducted by two independent data collectors and any discrepancies were resolved through consensus. The retrospective dataset was prone to timing documentation errors, but this limitation was overcome by the combination with richly sampled prospective cohort. In addition, the studied cohort encompassed multiple disease states, ethnicities, suggesting the potential generalizability of the results. A combination of bootstrap analysis and visual predictive checks were used to assure the internal validity of the results, which was not always combined in other published studies ([154](#)).

Furthermore, the present analysis is the largest and the first of its type in the MENA population.

On the other hand, several limitations should be noted in this vancomycin population pharmacokinetic modeling study. The inaccuracies in vancomycin sampling times documentation as part of routine clinical practice could not be assessed in the retrospective dataset. A considerable number of imputations was needed for serum creatinine concentrations due to the retrospective nature of part of the studied cohort. Clinical diagnostic parameters such as APACHE II scores, cardiac index or pharmacotherapeutic/mechanical interventions, were not explored as possible covariates. Lastly, the present model was not validated externally on an independent dataset, warranting further external validation studies. Future studies that address these limitations are suggested.

In conclusion, vancomycin population pharmacokinetics was established in the adult non-dialysis MENA population. Vancomycin

parameter estimates in the present population were similar to the parameter estimates of other adult non-dialysis patients, implying that MENA- population-specific vancomycin dosing nomograms are not warranted. The results of the present PK analysis can be used in therapeutic drug monitoring in the MENA population.

#### 5.4 Thesis conclusions

The findings of this project addressed major vancomycin dosing and monitoring challenges in the MENA region. This work suggests the needs for improvement of the quality of vancomycin TDM practices, the maintenance of a 24-hr-AUC between 564.71-1255.98 mg.hr/L, and the implementation of peak-trough-based vancomycin TDM as three main strategies that will potentially improve health-care outcomes associated with intravenous definitive and empiric vancomycin treatment. The findings have important implications on developing strategies that will improve rationale TDM practices in Qatar, the MENA region and possibly worldwide.

Based on the findings of Phase I of the study, routine vancomycin TDM practices in Qatar were at many times judged to be inappropriate in relation to sampling time and post-analytical actions, which might have contributed to suboptimal clinical outcomes, prolonged hospitalizations and adverse events. The retrospective multicenter evaluation identified the exact TDM practice deficiencies that will guide health policymakers to establish setting-specific protocols to improve TDM practices.

Second, the findings of Phase II of this project are of national, regional, and international relevance. This is the first head-to-head pragmatic RCT that compares peak-trough-based and trough-only-based vancomycin TDM approaches. The results contribute to determining which vancomycin TDM approach is associated with the achievement of vancomycin AUC/MIC breakpoint of cure and superior clinical outcomes. These findings are of international relevance and contribute to answering controversies in the current literature. The population in Qatar is heterogeneous; the majority

being expatriates originating from Asia and the MENA region. This allowed identifying vancomycin AUC/MIC breakpoint of cure that is specific to the MENA region and the Asian populations. Compared to trough-only-based vancomycin TDM, peak-trough-based vancomycin TDM was associated with higher clinical success rate, shorter duration of hospitalization and less vancomycin dose requirements. Maintaining a 24-hr-AUC between 564.117-1255.98 mg.hr/L has been associated with cure in the present study.

Lastly, Phase III of this project was the first study to determine vancomycin population pharmacokinetic parameters in adult non-dialysis MENA population. Population-specific covariates that influenced vancomycin pharmacokinetics and plasma exposure were identified. The developed vancomycin population-specific model will allow population-specific calculations of vancomycin pharmacokinetic parameters in individual patients in clinical settings, which is an important tool in vancomycin dosing. Furthermore, the need for population-specific vancomycin dosing nomograms was assessed, depending on the extent of similarities between our population's vancomycin pharmacokinetic parameters and the other populations. Vancomycin population parameter estimates of the local population are similar to literature reported 2-compartment model estimates, suggesting the generalizability of the published dosing nomograms to the population in Qatar. Thus, the development of vancomycin population dosing nomograms specific to Qatar's population may not be required at this point.

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## APPENDICES

### Appendix I: Pharmacokinetic equations

#### 1- Vancomycin peak-trough-based TDM approach (pharmacokinetic method)

Pharmacokinetic parameter	IV bolus infusion	IV intermittent infusion
Eliminate rate constant	$K_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$	
Half-life	$\ln 2 / K_e$	
Volume of distribution	$V = D / (C_p - C_t)$	$V = [k_0(1 - e^{-k_e t'})] / \{k_e [C_p - (C_t e^{-k_e t'})]\}$
Clearance	$Cl = K_e V$	
New dosing regimen	$\tau = \ln C_{\max-ss} - \ln C_{\min-ss} / k_e$	$\tau = (\ln C_{\max-ss} - \ln C_{\min-ss}) / k_e + t'$
	$Dose = C_{\max-ss} V (1 - e^{-k_e \tau})$	$Dose = C_{ss-max} K_e V [(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$

$K_e$ : elimination rate constant;  $k_0$ : infusion rate;  $t_{1/2}$ : half-life;  $V$ : volume of distribution;  $Cl$ : clearance;  $D$ : dose;  $C_1$ : vancomycin concentration at time  $t_1$ ;  $C_2$ : vancomycin concentration at time  $t_2$ ;  $C_p$ : peak concentration;  $C_t$ : trough concentration;  $C_{\max-ss}$ : target steady-state peak concentration;  $C_{\min-ss}$ : target steady-state trough concentration;  $\tau$ : dosing interval;  $t'$ : infusion duration

2- Vancomycin trough-only-based TDM approach (linear method)

Dose only change	Dosing interval only change
<p>New dose=  <math>(C_{ss-min}/C_t)D_{old}</math></p>	<p>New dosing interval (<math>\tau_{new}</math>)=  <math>(C_{ss-min}/C_t) \tau_{old}</math></p>

$C_{min-ss}$ : target steady-state trough concentration;  $C_t$ : trough concentration;  $D_{old}$ : old dose

3- Lean body weight (LBW)

Male	Female
<p><math>LBW[kg] = (0.73 * Height[cm]) - 59.42</math></p>	<p><math>LBW[kg] = (0.65 * Height[cm]) - 50.74</math></p>

Reference: Burton ME, Chow MS, Platt DR, et. al. Accuracy of Bayesian and Sawchuk-Zaske dosing methods for gentamicin. *Clin Pharm.* 1986 Feb;5(2):143-

#### 4- Cockcroft-Gault Creatine clearance estimation (CrCl)

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$$\text{CrCl} = ((140 - \text{Age}) / (\text{Serum creatinine}(\text{mg/dl})) * (\text{Weight}(\text{kg}) / 72) * (0.86 \text{ if female})$$

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Reference: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

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#### 5- Covariate imputation by interpolation

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$$X_u = X_b + \{(X_a - X_b) / (t_a - t_b)\} (t_u - t_b)$$

---

$X_u$ : unknown value to be interpolated at timepoint  $t_u$ ;  $X_a$ :  $X_u$  predecessor value at time point  $t_a$ ;  $X_b$ :  $X_u$  successive value at time point  $t_b$

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## Appendix II: Ethical approvals



### Qatar University Institutional Review Board QU-IRB

November 2, 2016

Ms. Fatima Khalifa Al-Sulaiti  
Graduate Student  
College of Pharmacy  
Qatar University  
Tel.: 55915441  
Email: [fa091335@qu.edu.qa](mailto:fa091335@qu.edu.qa)

Dear Ms. Fatima Al-Sulaiti,

**Sub.: Research Ethics Expedited Approval / Graduate Student Project**  
**Ref.: Project titled, "Clinical and Economic Evaluation of Optimal Monitoring Parameters and Sampling Schemes for Vancomycin Therapeutic Drug Monitoring in Qatar"**

We would like to inform you that your application along with the supporting documents provided for the above proposal, has been reviewed by the QU-IRB, and having met all the requirements, has been granted research ethics Expedited Approval for one year effective from November 2<sup>nd</sup>, 2016 till November 1<sup>st</sup>, 2017.

**Documents reviewed:** QU-IRB Checklist, QU-IRB Application, Informed Consent, Other stakeholders' approvals, Informed Consent, data collection form, Responses to IRB queries

Please note that all approvals are valid for a period of one year and renewals should be sought one month prior to the expiry date to ensure timely processing and continuity. Moreover, any changes/modifications to the original submitted protocol should be reported to the committee to seek approval prior to continuation.

Your Research Ethics Approval No. is: **QU-IRB 671-EA/16**  
Kindly refer to this number in all your future correspondence pertaining to this project.

Best wishes,

*K. Alali*

Dr. Khalid Al-Ali  
Chairperson, QU-IRB



Ref No: MRC1409/2016  
Date: 16 November 2016

**Dr. Ahmed ElZubair Satti,**  
Clinical Pharmacist  
Al Khor Hospital

Dear Dr. Satti,

**Research Protocol #16348/16: "Retrospective Utilization of Routine Therapeutic Drug Monitoring Data for Population Pharmacokinetic Analyses and the Evaluation of the Status, Appropriateness and Outcomes of Therapeutic Drug Monitoring Service in Qatar"**

The above titled Research Proposal submitted to the Medical Research Center has been reviewed and classified as "Exempt" under SCH guidelines "**Category 3: Research involving the collection or study of existing data, documents, records as the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects**" approval is granted from 16 November 2016.

This research study should be conducted in full accordance with all the applicable sections of the rules and regulations for research at HMC and you should notify the Medical Research Center immediately of any proposed protocol changes that may affect the 'exempt' status of your research proposal. It is the Principal Investigator's responsibility to obtain review and continued approval of the proposal if there is any modification to the approved protocol.

Documents reviewed by the Research Center:

- Research Proposal
- Data Collection sheet (Jan 2014 – September 2016)

A study progress report should be submitted bi-annually and a final report upon study's completion.

We wish you all success and await the results in due course.

Yours sincerely,

  
**Prof. Ibrahim Al Janahi**  
Executive Director of Research  
Medical Research Center

- Cc:
1. Ahmed Awaisu (LPI)
  2. Hani Abdelaziz\* (Co-PI)
  3. Rizwan Imanullah\* (Co-PI)
  4. Fatma Al Sulaiti (Co-PI)
  5. Ahmed ElZubair Satti\* (Co-PI)

Tel: (+974) 4439 2440  
Fax: (+974) 44395402  
research@hmc.org.qa

P.O.Box 3050  
Doha, Qatar  
www.hmc.org.qa

## Appendix III: Research consent form

### نموذج الموافقة على الاشتراك في بحث علمي RESEARCH CONSENT FORM

	
<b>1. Title of research</b>	1. عنوان البحث
Clinical and Economic Evaluation of Optimal Monitoring Parameters and Sampling Schemes for Vancomycin Therapeutic Drug Monitoring in Qatar	التقييم السريري والاقتصادي لأنسب معايير الرصد وأفضل أنظمة سحب العينات لرصد التأثيرات العلاجية لعقار الفانكوميسين على وظائف الجسم في دولة قطر.
<b>2. Principal Investigator</b>	2. الباحث الأساسي
Dr. Ahmed Awaisu, Qatar University	الدكتور أحمد عويسو، جامعة قطر
<b>3. Why are we inviting you to join this research?</b>	3. ما هو سبب دعوتنا لك للمشاركة في هذا البحث؟
<ul style="list-style-type: none"> <li>The investigator and colleagues at Hamad Medical Corporation (HMC) and Qatar University are conducting this research.</li> <li>We are inviting you to join because your physician has prescribed vancomycin to treat your infection and your health condition is stable.</li> </ul>	<ul style="list-style-type: none"> <li>يجري الباحث وزملاؤه في مؤسسة حمد الطبية وجامعة قطر هذا البحث.</li> <li>ندعوك للمشاركة في هذا البحث الذي نجره لأن طبيبك المعالج قام بوصف عقار الفانكوميسين لعلاجك من العدوى وحالتك الصحية مستقرة.</li> </ul>
<b>4. What should you know about this research?</b>	4. ما هي المعلومات التي يجب أن تعرفها عن الدعوة؟
<ul style="list-style-type: none"> <li>We will explain the research to you</li> <li>Whether or not you join is your decision (you can accept or refuse no matter who is inviting you to participate)</li> <li>Please feel free to ask questions or mention concerns before deciding, or during or after the research</li> <li>You can say yes but change your mind later</li> <li>Your decision to join this research or not will not affect your treatment/care process by any means</li> </ul>	<ul style="list-style-type: none"> <li>سنشرح لك البحث شرحًا وافيًا.</li> <li>قرار مشاركتك في البحث أو عدم مشاركتك يرجع لك وحدك (يمكنك قبول الدعوة أو رفضها بغض النظر عن الجهة التي ندعوك للمشاركة).</li> <li>لك سطلق الحرية في طرح أية استفسارات أو مخاوف قبل اتخاذ قرارك أو أثناء أو بعد المشاركة في البحث.</li> <li>يمكنك قبول الدعوة وتغيير رأيك لاحقًا.</li> <li>إن بאתر قرارك بقبول أو رفض المشاركة في هذا البحث على علاجك أو رعايتك بأي شكل من الأشكال.</li> </ul>
<b>5. Who can you talk to?</b>	5. ما هي الجهة التي يمكنك مراجعتها؟
If you have questions or concerns, or if you think the research has hurt you, talk to the research team at:	إذا كان لديك أية استفسارات أو مخاوف أو إذا ما ارتأيت أن البحث قد تسبب لك في أي إهداء، يمكنك مراجعة فريق البحث:

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<p><b>1. Dr. Ahmed Awaisu</b> College of Pharmacy, Qatar University Telephone: (+974) 4403 5596 Email: <a href="mailto:aaawaisu@qu.edu.qa">aaawaisu@qu.edu.qa</a></p> <p><b>2. Dr. Hani Abdelaziz</b> Pharmacy Department, Al Wakra Hospital Telephone: (+974) 55742412 Email: <a href="mailto:HAziz2@hamad.qa">HAziz2@hamad.qa</a></p> <p><b>3. Ahmed Elzubair Satti Elzubair</b> Pharmacy Department, Al Khor Hospital Mobile: (+974) 66520473 E-mail: <a href="mailto:aelzubair@hamad.qa">aelzubair@hamad.qa</a></p> <p><b>4. Dr. Rakesh Parakadavathu</b> Specialist, Infectious Disease, Hamad General Hospital Mobile: (+974) 70297357 Email: <a href="mailto:tparakadavathu@hamad.qa">tparakadavathu@hamad.qa</a></p> <p>If you have questions about your rights as a volunteer, or you want to talk to someone outside the research team, please contact:</p> <ul style="list-style-type: none"> <li>HMC Medical Research Centre at <a href="mailto:irb@hamad.qa">irb@hamad.qa</a></li> </ul>	<p>1. دكتور أحمد عويسو كلية الصيدلة، جامعة قطر رقم الهاتف: +97444035596 البريد الإلكتروني: <a href="mailto:aaawaisu@qu.edu.qa">aaawaisu@qu.edu.qa</a></p> <p>2. دكتور هاني عبد العزيز قسم الصيدلية بمستشفى الوكرة رقم الهاتف: +97455742412 البريد الإلكتروني: <a href="mailto:HAziz2@hamad.qa">HAziz2@hamad.qa</a></p> <p>3. أحمد الزبير ساتي الزبير قسم الصيدلية بمستشفى الخور الهاتف الجوال: +97466520473 البريد الإلكتروني: <a href="mailto:aelzubair@hamad.qa">aelzubair@hamad.qa</a></p> <p>4- دكتور ريكيش پاراكادافاثو طبيب اختصاصي للأمراض المعدية بمستشفى حمد العام الهاتف الجوال: +97470297357 البريد الإلكتروني: <a href="mailto:tparakadavathu@hamad.qa">tparakadavathu@hamad.qa</a></p> <p>إذا كان لديك أية استفسارات عن حقوقك كمتطوع أو كانت لديك رغبة في معاناة شخص لا ينتمي لفريق البحث، يرجى مراجعة:</p> <ul style="list-style-type: none"> <li>مركز البحوث الطبية بمؤسسة حمد الطبية على: <a href="mailto:irb@hamad.qa">irb@hamad.qa</a></li> </ul>
<p><b>6. Why are we doing the research?</b></p>	<p>6. ما هي أسباب إجراء البحث؟</p>
<ul style="list-style-type: none"> <li>Vancomycin is an antibiotic that is widely used to treat bacterial infections.</li> <li>Therapeutic drug monitoring of vancomycin is an integral part in ensuring the attainment of positive clinical outcomes and minimizing adverse events associated with the drug.</li> <li>Therapeutic drug monitoring of vancomycin involves measuring vancomycin concentrations in the blood and giving vancomycin dose to the patient based on vancomycin drug concentrations in the blood.</li> <li>Albeit it being a more than 50 years old drug, vancomycin still poses many questions regarding its optimal dosing and monitoring strategies.</li> <li>This study will identify the best vancomycin dosing and monitoring approaches that will contribute to better patient health and decreased</li> </ul>	<ul style="list-style-type: none"> <li>عقار الفانكوميسين هو مضاد حيوي شائع الاستخدام في علاج ومكافحة العدوى البكتيرية.</li> <li>رصد التأثيرات العلاجية لعقار الفانكوميسين على وظائف الجسم جزء لا يتجزأ من إجراءات ضمان تحقيق نتائج سريرية إيجابية والحد من الآثار الجانبية للمصاحبة لاستخدام هذا الدواء.</li> <li>رصد التأثيرات العلاجية لعقار الفانكوميسين على وظائف الجسم يتطلب على قياس تراكيز الفانكوميسين في الدم وإعطاء جرعة الفانكوميسين للمريض بناءً على تراكيز عقار الفانكوميسين في الدم.</li> <li>على الرغم من أن هذا الدواء مستخدم منذ أكثر من 50 عامًا ولكن لا يزال الفانكوميسين مثيلاً للتساؤلات بشأن النسب وأفضل استراتيجيات إعطاء الجرعات والرصد.</li> <li>يساعد هذا البحث أفضل مناهج إعطاء الجرعات والرصد التي ستسهم في تحسين صحة المرضى وخفض تكاليف نظام الرعاية الصحية.</li> </ul>

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costs to the healthcare system. • We will use your blood samples (to measure vancomycin concentrations) and medical information to achieve the goals of this study.	• ستستخدم عينات الدم (لقياس تركيزات الفانكوميسين في الدم) والمعلومات الطبية لتحقيق أهداف هذا البحث.
<b>7. How long will the research take?</b>	7. ما هي المدة التي سيستغرقها البحث؟
- We think that you will be in the research as long as your physician chooses to keep you on vancomycin treatment. - We will follow-up with you 30 days after completing treatment with vancomycin. - We expect the research to last for 1.5-2 years.	- نرى أن مشاركتك ستستمر في البحث طالما يقرر طبيبك المعالج استمرار علاجك باستخدام عقار الفانكوميسين. - ستتابع حالتك لمدة 30 يوماً بعد انتهاء علاجك بعقار الفانكوميسين. - نتوقع أن يستغرق هذا البحث مدة عام ونصف إلى عامين.
<b>8. How many people will take part?</b>	8. كم عدد المشاركين في البحث؟
We plan to study 150 persons from HMC.	نعتزم إجراء البحث على 150 شخصاً من مؤسسة حمد الطبية.
<b>9. What happens if you take part?</b>	9. ما هي الإجراءات المطلوبة في حالة المشاركة في البحث؟
If you agree to join this study, we will ask you to kindly do the following: 1- Ask your permission to access your medical records. 2- While receiving your treatment in the hospital, you will be "randomized" into one of two study groups. Each group will include 75 patients. "Randomized" means that you are placed into one of the two groups by chance. It is like flipping a coin. Neither you nor the researchers choose which group you will be in. You will have a 50% chance of being place in a specific group. 3- These four blood samples will be drawn as follows: (1) first sample at 1 hour after the third dose; (2) second sample at 4 hours after the third dose; (3) third sample at 6 - 8 hours after the third dose and the; (4) fourth sample will be taken 30 minutes before the fourth dose of vancomycin is given to you. 4- Based on the results, your vancomycin dose will be tailored to achieve certain target concentrations. The vancomycin dose will be	في حالة موافقتك على الانضمام لهذا البحث، سنطلب منك التكرم بإجراء ما يلي: 1- سنطلب منك الإذن بالنفاد إلى سجلاتك الطبية. 2- بينما تتلقى العلاج في المستشفى، سيتم ضمك "عشوائياً" لإحدى مجموعتي البحث التي تضم كل منهما 75 مريضاً. والمقصود بكلمة "عشوائياً" أنه سيتم وضعك في إحدى المجموعتين عن طريق الصدفة. فلن تتمكن أنت ولا الباحثون من اختيار المجموعة التي ستضم لها وبالتالي ستساوى حظوظك في الانضمام لأي من المجموعتين. 3- سنقوم بسحب أربع عينات دم كالتالي: (1) العينة الأولى بعد ساعة من تناول الجرعة الثالثة. (2) والعينة الثانية بعد 4 ساعات من تناول الجرعة الثالثة. (3) والعينة الثالثة بعد 6-8 ساعات من تناول الجرعة الثالثة. (4) والعينة الرابعة قبل 30 دقيقة من تناول جرعة عقار الفانكوميسين. 4- بناءً على هذه النتائج، سيتم ضبط جرعة الفانكوميسين بشكل يؤدي إلى تحقيق تركيزات معينة مسبقة. فسيتم ضبط جرعة الفانكوميسين خصيصاً لتلائم حالتك وتعديلها باستخدام أسلوب من أساليب راسخين ثبت نجاحهما في جميع أنحاء العالم ونقوم بالمقارنة بينهما في هذه التجربة العلمية وكلاهما آمنين وقياسيين في مجال الرعاية. 5- إذا كانت مستويات الدم في المعدل المسبقة لتركيزات الفانكوميسين،



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<p>tailored to you and adjusted using one of the two well-established and proven methods worldwide, that we are comparing in this trial. Both methods are safe and are standard of care.</p> <p>5- If your blood levels are at target vancomycin concentrations, we will monitor your blood concentrations every 24-48 hours.</p> <p>6- We will follow-up with you 30 days after completing treatment with vancomycin.</p> <p>The clinical pharmacist will adjust vancomycin doses. Laboratory phlebotomist will draw blood samples from the patients, which is part of routine practice in HMC.</p>	<p>سيقوم برصد تراكيز الدم لديك كل 24-48 ساعة. 6- ستتابع حالتك بعد 30 يوماً من انتهاء علاجك بعقار الفانكوميسين.</p> <p>سيقوم الصيدلي السريري بضبط وتعديل جرعات الفانكوميسين بينما سيقوم فني مختبرات متخصص في قسط الأوردة بسحب عينات الدم من المرضى. وهو إجراء روتيني في مؤسسة حمد الطبية.</p>
<p><b>10. What if the subject cannot provide consent?</b></p>	<p>10. ما هو الإجراء المتبع إذا كان المعني غير قادر على إعطاء موافقته؟</p>
<p>- If the subject is critically ill, unconscious or mentally disabled, his/her legal guardian (i.e. a family member) will be reached to provide consent.</p> <p>- If the family member/legal guardian provides consent, the patient will be enrolled in the trial. His/her data will only be used if they consent after recovery from their critical health or mental status.</p> <p>- If no recovery from the mental/health status occurs by the end of trial, the family member/legal guardian consent will be considered official approval to proceed with using the patient's data.</p> <p>- Only if a patient is in coma or lacks the mental capacity to make an informed decision and a family member/legal guardian cannot be reached by any means, a waiver of consent may be requested if the attending physician sees that the risk to the subject is low to no risk (in cases where blood samples are drawn from patients as part of routine care, and the same specimen can be used to measure vancomycin concentrations).</p>	<p>- إذا كان المريض يعاني من مرض خطير أو فاقد الوعي أو معاق ذهنياً، سيتم الاتصال بالوصي القانوني (كأحد أفراد العائلة) للحصول على موافقته.</p> <p>- في حالة الحصول على الإذن من أحد أعضاء العائلة \ الوصي القانوني سيتم تسجيل المريض في التجربة ولن تستخدم بياناته إلا في حالة موافقته على ذلك بعد تعافيه من حالته الصحية أو الذهنية الحرجة.</p> <p>- في حالة عدم تعافيه من حالته الصحية أو الذهنية بنهاية التجربة، سيتم اعتبار إذن فرد العائلة\ الوصي القانوني بمثابة موافقة رسمية للشروع في استخدام بيانات المريض.</p> <p>- إذا كان المريض في غيبوبة أو فاقد الأهلية العقلية والتميز لاتخاذ القرار مع تعذر التوصل إلى أحد أفراد العائلة / الوصي القانوني بأي وسيلة، يمكن طلب الإغفاء من الحصول على الموافقة إذا رأى الطبيب المعالج انخفاض أو لعدام الخطر على الحالة (في الحالات التي يتم فيها سحب عينات الدم من المرضى كجزء من الرعاية الروتينية، ويمكن استخدام نفس العينة لقياس تراكيز عقار الفانكوميسين).</p>

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<p><b>11. Could the research be bad for you?</b></p>	<p><b>11. هل يمكن أن يعرضك البحث لأي ضرر؟</b></p>
<ul style="list-style-type: none"> <li>- Anticipated risks to participants are similar to those of usual care. This is because the study is comparing well established vancomycin therapeutic drug monitoring approaches.</li> <li>- Risks are pertinent to phlebotomy, which will include pain, bruising or phlebitis which are very rare. As per HMC policies, the blood samples will be drawn by expert laboratory professional staff at HMC at very strict infection control condition.</li> <li>- Procedures involved in this research might be dangerous for pregnant women and/or fetuses. You should not be pregnant while in this research. If your physician suspects that you may be pregnant, a pregnancy test will be done to assure that the patient is not pregnant. Please tell the research team if you are pregnant or think that you may be pregnant.</li> </ul>	<ul style="list-style-type: none"> <li>- المخاطر المتوقعة حدوثها للمشاركين في هذا البحث مماثلة لمخاطر الرعاية العادية وذلك نظرًا لأن البحث يقارن بين منهجيات راسخة لرصد تأثيرات عقار الفانكوميسين العلاجية على وظائف الجسم.</li> <li>- وتتعلق هذه المخاطر بقصد الوريد بما يشمل الألم أو الكدمات أو الالتهابات الوريدية النادرة للغاية. بمقتضى سياسات مؤسسة حمد الطبية سيتم سحب عينات الدم بواسطة طاقم تحاليل محترف من ذوي الخبرة في مؤسسة حمد الطبية مع اتباع شروط صارمة جدًا لمكافحة العدوى.</li> <li>- قد تشكل إجراءات هذا البحث خطرًا على الحوامل و/أو الأجنة وبالتالي، يجب ألا تكوني حاملًا أثناء المشاركة في هذا البحث. فإذا شك الطبيب بأنك حامل، سيتم إجراء اختبار حمل للتأكد من عدم وجود حمل. يرجى إخطار فريق البحث إذا كنت حاملًا أو تعتقدي إمكانية وجود حمل.</li> </ul>
<p><b>12. Could the research be good for you?</b></p>	<p><b>12. هل يمكن أن تستفيد من هذا البحث؟</b></p>
<ul style="list-style-type: none"> <li>- We cannot promise any benefit to you or to others from you joining this research. However, possible benefits include faster cure rates, shorter length of hospital stay, fewer side effects from vancomycin treatment, less treatment failures and the need for change of therapy from vancomycin to another drug.</li> <li>- The proposed study will be an invaluable tool as it will aid in answering a currently hugely debatable topic: What is the best way to monitor and dose vancomycin, to achieve maximal clinical outcomes? Also, the study will potentially result in developing vancomycin-dosing nomograms that are specific to the multiethnic widely diverse population in Qatar. We anticipate that the results will significantly contribute to maximize efficacy, minimize side effects and decrease costs in Qatar and worldwide.</li> </ul>	<ul style="list-style-type: none"> <li>- لا نستطيع أن نعدك بتحقيق أي استفادة سواء لك أو للآخرين من المشاركة في هذا البحث، ولكن يحتمل أن يسهم هذا البحث في تسريع معدلات الشفاء، وتقليل مدة البقاء في المستشفى، والحد من الآثار الجانبية للعلاج بعقار الفانكوميسين، والحد من فشل العلاج والحاجة لتغير العلاج من الفانكوميسين إلى نوع آخر من العقاقير.</li> <li>- سيصبح هذا البحث المقترح وسيلة علاجية لا تقدر بثمن لأنه سيساعد في حسم المسألة الخلافية المثارة حاليًا بشكل كبير: ما هي أفضل طريقة لرصد وتحديد جرعة الفانكوميسين لتحقيق أفضل النتائج السريرية؟ وعلاوة على ذلك، فمن المرجح أن يتسبب البحث في تطوير المخططات الميانية لتحديد جرعات الفانكوميسين المخصصة للتركيبات السكانية متعددة العرقيات وشديدة التنوع في دولة قطر. ونتوقع أن تسهم النتائج إسهامًا كبيرًا في تحقيق أقصى قدر من الكفاءة والحد من الآثار الجانبية وخفض التكاليف في دولة قطر وجميع دول العالم.</li> </ul>

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<p><b>13. What happens to information about you?</b></p>	<p>13. كيف سيتم استخدام المعلومات الخاصة بك؟</p>
<p>We will make efforts to secure information about you. This includes using a code to identify you in our records instead of using your name. We will not identify you personally in any reports or publications about this research.</p> <p>We cannot guarantee complete secrecy, but we will limit access to information about you. Only people who have a need to review information will have access. These people might include:</p> <ul style="list-style-type: none"> <li>• Members of the research team whose work is related to the research or to protecting your rights and safety</li> <li>• Representatives of the Qatar Supreme Council of Health and HMC Medical Research center who make sure the study is done properly and that your rights and safety are protected</li> <li>• Your multidisciplinary clinical team</li> </ul> <p>Your samples will be kept and used: in Qatar only. Your samples will be used for the purposes of this study only. Any samples left over will be destroyed immediately after measuring vancomycin blood concentrations in HMC laboratories.</p>	<p>سنبذل كافة الجهود لتأمين سرية بياناتك بما يتضمن استخدام رمز للتعرف على هويتك في سجلاتنا بدلاً من استخدام اسمك بشكل صريح ولن نذكر اسمك في أي تقارير أو منشورات تخص هذا البحث.</p> <p>لا يمكننا ضمان سرية البيانات بشكل مطلق، إلا أننا سنحدّ من إمكانية الوصول إلى بياناتك لتكون مقصورة على الأشخاص الذين يحتاجون إلى مراجعة المعلومات وقد يشمل هؤلاء الأشخاص:</p> <ul style="list-style-type: none"> <li>• أعضاء فريق البحث ممن يرتبط عملهم بالبحث أو بحماية حقوقك وسلامتك.</li> <li>• ممثلو المجلس الأعلى للصحة في دولة قطر ومركز البحوث الطبية بمؤسسة حمد الطبية للتأكد من تنفيذ البحث بالشكل الصحيح مع حماية حقوقك وسلامتك.</li> <li>• الفريق الطبي متعدد التخصصات</li> </ul> <p>سيتم الاحتفاظ بالعينات المأخوذة منك واستخدامها في دولة قطر وبحصر استخدامها في هذا البحث فقط وسيتم تدوير أي عينات متبقية بمجرد قياس مستوى تركيز الفانكوميسين في الدم في مختبرات مؤسسة حمد الطبية.</p>
<p><b>14. What if you don't want to join?</b></p>	<p>14. ماذا لو كنت لا تريد المشاركة في البحث؟</p>
<p>You can say no and we will not hold it against you.</p>	<p>يمكنك رفض المشاركة في البحث دون أن يستخدم ذلك ضدك.</p>
<p><b>15. What if you join but change your mind?</b></p>	<p>15. ماذا لو شاركت في البحث ثم غيرت رأيك؟</p>
<p>You can stop participating at any time and we will not hold it against you.</p> <p>We will tell you about any new information that might affect your health or welfare, or might affect your willingness to continue in the research.</p> <p>If you stop participating, we will use information that we have already collected about you as long as you agree.</p>	<p>يمكنك التوقف عن المشاركة في أي وقت دون أن يستخدم ذلك ضدك.</p> <p>وسنقوم بإخطارك بما يستجد من معلومات قد تؤثر على صحتك أو قد تؤثر على رغبتك في الاستمرار في البحث.</p> <p>إذا قررت التوقف عن المشاركة سنستخدم المعلومات التي جمعناها منك بالفعل طالما قبلت ذلك.</p>
<p><b>16. What else should you know?</b></p>	<p>16. هل هناك معلومات أخرى يجب معرفتها؟</p>

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<p>This research is funded by Qatar University</p> <p>If you are injured as a direct result of research procedures, contact the investigator and appropriate care will be made available at HMC. If you seek care outside of HMC, such care will be at your expense. Compensation is not available in case of injury.</p>	<p>هذا البحث ممول من جامعة قطر.</p> <p>إذا أصبت كنتيجة مباشرة لإجراءات البحث، يرجى الاتصال بالباحث وسيتم توفير الرعاية المناسبة لك في مؤسسة حمد الطبية. أما إذا كنت ترغب في تلقي الرعاية خارج مؤسسة حمد الطبية، سيكون ذلك على نفقتك الشخصية ولن يتم تعويضك مادياً في حالة الإصابة.</p>
<p><b>17. Additional Choices</b></p>	<p>17. الخيارات الإضافية</p>
<p>We would like your permission to contact you about participating in future studies. You may still join this study even if you do not permit future contact. You may also change your mind about this choice. Please initial your choice below:</p> <p>_____ YES, you may contact me</p> <p>_____ NO, you may NOT contact me</p>	<p>نود الحصول على موافقتك على الاتصال بك للمشاركة في الأبحاث المستقبلية. ويمكنك الانكفاء بالمشاركة في هذه البحث حتى لو لم تسمح بالاتصال بك في المستقبل. كما يمكنك تغيير رأيك بشأن هذا الاختيار. يرجى التوقيع بجوار اختيارك:</p> <p>_____ نعم، يمكنكم الاتصال بي</p> <p>_____ لا، لا يمكنكم الاتصال بي</p>

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Signature Page for Capable Adult	صفحة توقيع البالغ القادر
Volunteer	المتطوع
<i>I voluntarily agree to join the research described in this form.</i>	أوافق طوعاً على المشاركة في البحث الوارد في هذا النموذج بمحض إرادتي.
Printed Name of Volunteer	اسم المتطوع بالأحرف الواضحة
Signature of Volunteer      Date	توقيع المتطوع      التاريخ
Person Obtaining Consent	الشخص الحاصل على الموافقة
<i>I document that:</i>	أقر بما يلي:
<ul style="list-style-type: none"> <li><i>I (or another member of the research team) have fully explained this research to the volunteer.</i></li> <li><i>I have personally evaluated the volunteer's understanding of the research and obtained their voluntary agreement.</i></li> </ul>	<ul style="list-style-type: none"> <li>لقد قمت (أنا أو عضو آخر من فريق البحث) بشرح البحث للمتطوع شرحاً وافياً.</li> <li>لقد قمت شخصياً بتقييم مدى فهم المتطوع للبحث والحصول على موافقته طوعاً دون إكراه.</li> </ul>
Printed Name of Person Obtaining Consent	اسم الحاصل على الموافقة بالأحرف الواضحة
Signature of Person Obtaining Consent      Date	توقيع الحاصل على الموافقة      التاريخ
Witness (if applicable)	الشاهد (إن وجد)
<i>I document that the information in this form (and any other written information) was accurately explained to the volunteer, who appears to have understood and freely given Consent to join the research.</i>	أشهد بأن المعلومات الواردة في هذا النموذج (وأية معلومات أخرى مكتوبة) قد شُرحَت بدقة للمتطوع الذي بدى عليه فهم البحث وقام بمنح موافقته للمشاركة في البحث بمحض إرادته.
Printed Name of Witness	اسم الشاهد بالأحرف الواضحة
Signature of Witness      Date	توقيع الشاهد      التاريخ

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Signatures: Adult Unable to Consent	توقيعات: البالغ غير القادر على الموافقة
Legally Authorized Representative	الممثل القانوني
<i>I voluntarily agree for the person named below to join the research described in this form.</i>	أوافق طوعاً على مشاركة الشخص المذكور اسمه أدناه في البحث الوارد في هذا النموذج بمحض إرادتي.
Printed Name of Volunteer	اسم المتطوع بالأحرف الواضحة
Printed Name of Representative Relationship	اسم الممثل القانوني بالأحرف الواضحة علاقته المتطوع
Signature of Representative Date	توقيع الممثل القانوني التاريخ
Person Obtaining Consent	الشخص الحاصل على الموافقة
<i>I document that:</i>	أقر بما يلي:
<ul style="list-style-type: none"> <li><i>I (or another member of the research team) have fully explained this research to the representative.</i></li> <li><i>I have personally evaluated the representative's understanding of the research and obtained their voluntary agreement.</i></li> </ul>	<ul style="list-style-type: none"> <li>لقد قمت (أنا أو عضو آخر من فريق البحث) بشرح البحث للممثل القانوني شرحاً وافياً.</li> <li>لقد قمت شخصياً بتقييم مدى فهم الممثل القانوني للبحث والحصول على موافقته طوعاً دون إكراه.</li> </ul>
Printed Name of Person Obtaining Consent	اسم الحاصل على الموافقة بالأحرف الواضحة
Signature of Person Obtaining Consent Date	توقيع الحاصل على الموافقة التاريخ
Witness (if applicable)	الشاهد (إن وجد)
<i>I document that the information in this form (and any other written information) was accurately explained to the representative, who appears to have understood and freely given consent.</i>	أشهد بأن المعلومات الواردة في هذا النموذج (وأية معلومات أخرى مكتوبة) قد شرحت بدقة للممثل القانوني الذي يبدو عليه فهم البحث وقام بمنح موافقته بمحض إرادته.
Printed Name of Witness	اسم الشاهد بالأحرف الواضحة
Signature of Witness Date	توقيع الشاهد التاريخ