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ORIGINAL RESEARCH ARTICLE

Clinical and Pharmacokinetic Outcomes of Peak–Trough-Based Versus Trough-Based Vancomycin Therapeutic Drug Monitoring Approaches: A Pragmatic Randomized Controlled Trial

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Abstract

Background Vancomycin therapeutic drug monitoring (TDM) is based on achieving 24-h area under the concentration–time curve to minimum inhibitory concentration cure breakpoints (AUC_{24}/MIC). Approaches to vancomycin TDM vary, with no head-to-head randomized controlled trial (RCT) comparisons to date.

Objectives We aimed to compare clinical and pharmacokinetic outcomes between peak–trough-based and trough-only-based vancomycin TDM approaches and to determine the relationship between vancomycin AUC_{24}/MIC and cure rates.

Methods A multicentered pragmatic parallel-group RCT was conducted in Hamad Medical Corporation hospitals in Qatar. Adult non-dialysis patients initiated on vancomycin were randomized to peak–trough-based or trough-only-based vancomycin TDM. Primary endpoints included vancomycin AUC_{24}/MIC ratio breakpoint for cure and clinical effectiveness (therapeutic cure vs therapeutic failure). Descriptive, inferential, and classification and regression tree (CART) statistical analyses were applied. NONMEM.v.7.3 was used to conduct population pharmacokinetic analyses and AUC_{24} calculations.

Results Sixty-five patients were enrolled [trough-only-based-TDM ($n = 35$) and peak–trough-based-TDM ($n = 30$)]. Peak–trough-based TDM was significantly associated with higher therapeutic cure rates compared to trough-only-based TDM [76.7% vs 48.6%; p value = 0.02]. No statistically significant differences were observed for all-cause mortality, neutropenia, or nephrotoxicity between the two groups. Compared to trough-only-based TDM, peak–trough-based TDM was associated with less vancomycin total daily doses by 12.05 mg/kg/day (p value = 0.027). CART identified creatinine clearance (CL_{CR}), AUC_{24}/MIC, and TDM approach as significant determinants of therapeutic outcomes. All patients [$n = 19$,100%] with $CL_{CR} \leq 7.85$ L/h, $AUC_{24}/MIC \leq 1256$, who received peak–trough-based TDM achieved therapeutic cure. $AUC_{24}/MIC > 565$ was identified to be correlated with cure in trough-only-based TDM recipients [$n = 11$,84.6%]. No minimum AUC_{24}/MIC breakpoint was detected by CART in the peak–trough-based group.

Conclusion Maintenance of target vancomycin exposures and implementation of peak–trough-based vancomycin TDM may improve vancomycin-associated cure rates. Larger scale RCTs are warranted to confirm these findings.

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Key points

Compared to trough-based vancomycin TDM, peak–trough-based vancomycin TDM was associated with a higher clinical success rate and less vancomycin dose requirements.

Maintaining AUC_{24}/MIC between 565 and 1256 has been associated with cure.

1 Introduction

Therapeutic drug monitoring (TDM) of vancomycin is essential in ensuring the attainment of positive clinical outcomes and minimizing toxicity [1]. Vancomycin clinical pharmacokinetic parameters exhibit large inter-individual variability even with identical dosing regimens [2]. Traditionally, steady-state vancomycin peak ($C_{max,ss}$) and trough ($C_{trough,ss}$) concentrations were measured for vancomycin TDM. In 2009, a paradigm shift in clinical vancomycin dosing and monitoring practices emerged, 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) [3]. Based on limited clinical data and animal studies, vancomycin was considered 'concentration-independent' and thus $C_{max,ss}$ monitoring was no longer recommended. Additionally, a 24-h area under the concentration–time curve (AUC_{24}) to minimum inhibitory concentration (MIC) ratio (AUC_{24}/MIC) of ≥ 400 was defined as the target surrogate to attain clinical effectiveness. These guidelines recommended $C_{trough,ss}$ monitoring as a surrogate for achieving AUC_{24}/MIC ≥ 400 with a value of 15–20 mg/L as an acceptable therapeutic range.

Published evidence after 2009 called into question the recommended target ratio (AUC_{24}/MIC ≥ 400) [4], as different AUC/MIC ratios have been found to achieve clinical effectiveness [5–7]. This reported variability in AUC/MIC breakpoints may be attributed to the genetic variability between methicillin-resistant *Staphylococcus aureus* (MRSA) strains across different geographical areas [8–18], the differences in MRSA site of infection, and the variability of the populations studied in terms of comorbidities and ethnicities [19]. Hence, the generalizability of the published literature remains limited to different disease states, geographical regions, and populations. Furthermore, recent studies questioned the use of $C_{trough,ss}$ as an indicator of AUC_{24}/MIC optimal exposure, as discrepancies between optimal AUC_{24} exposures and the associated trough concentrations have been reported [2, 20–24]. The superior clinical utility of multiple-concentration-based vancomycin dosing approaches compared to trough-only guided dosing has been suggested [21–23]. One of those approaches is peak–trough-based pharmacokinetic dosing [20, 23, 25]. Collectively, these studies raised concerns regarding the optimal vancomycin AUC_{24}/MIC breakpoint for cure, and the best vancomycin TDM approach that would result in the attainment of the optimal AUC_{24}/MIC ratio associated with clinical effectiveness.

The use of vancomycin in the treatment of serious Gram-positive infections has become very challenging in Asia, including the Middle East and North Africa (MENA) region [16, 26, 27]. A meta-analysis of 91 studies exploring the epidemiology of vancomycin intermediate-resistant *S.aureus* (VISA) strains during 1997 and 2014, reported higher VISA incidence rates in Asia, including MENA, compared to other regions [26]. Given that suboptimal antimicrobial therapy of MRSA contributes to the emergence of resistant strains [27], these findings highlight the potentially high prevalence of inadequate vancomycin treatment in MENA. This can be attributed to non-adherence to clinical practice guidelines or the limited generalizability of vancomycin AUC_{24}/MIC targets reported elsewhere. Genetic and epidemiologic diversity between MRSA clones across various geographical regions and time-points have been reported worldwide, including MENA [12–18]. However, the currently applied vancomycin dosing nomograms in the MENA region are based on published Western vancomycin pharmacokinetic–pharmacodynamic targets, due to the lack of studies reporting MENA-specific targets. Expatriates from different MENA and Asian countries constitute the majority of Qatar's population, with nationals reported to be < 15% [28, 29]. Therefore, we aimed to explore MENA-specific pharmacokinetic–pharmacodynamic vancomycin targets to understand the reasons for vancomycin treatment failures in the MENA region.

Although the 2009 consensus guidelines recommend trough-only monitoring [3], to the best of our knowledge, no prospective randomized controlled trials (RCTs) have been conducted to compare the clinical and pharmacokinetic outcomes between the traditional peak–trough-based and the trough-only-based vancomycin TDM approaches. Additionally, the vancomycin AUC_{24}/MIC cure breakpoint in MENA-specific populations and bacterial strains has not yet been studied. Therefore, this prospective parallel-group pragmatic multicenter RCT was conducted to compare the clinical and pharmacokinetic outcomes of peak–trough-based and trough-only-based vancomycin TDM approaches and to evaluate the relationship between vancomycin AUC_{24}/MIC ratios and cure in the MENA population.

2 Methods

2.1 Study Design and Setting

A multicenter pragmatic two parallel-group RCT was conducted in three tertiary care hospitals under Hamad Medical Corporation (HMC) in Qatar—Al-Wakrah Hospital (AWH), Al-Khor Hospital (AKH), and Hamad General Hospital (HGH).

2.2 Study Population and Sample Size Calculation

Inclusion criteria included hospitalized adults (≥18 years) with suspected/confirmed staphylococcal or other Gram-positive infection requiring treatment with vancomycin for at least 3 days based on the attending physician's judgment. Exclusion criteria included renal instability [abrupt absolute increase in serum creatinine (SCr) ≥ 0.5 mg/dL from baseline or a percentage increase in SCr ≥ 50% within 48 h]; end-stage renal disease; transplant; immunosuppression; active malignancy; receiving antineoplastic agents; HIV or absolute neutrophil counts < 1000 cells/mm^3; vancomycin allergy; history of recurrent resistant peritonitis; administration of < 4 doses of vancomycin or for < 72 h; vancomycin administration for post-surgical infection prophylaxis; pregnancy; subjects not able to undergo blood sampling per clinician judgment; anuria (urine output < 100 mL/day); symptomatic anemia; and hemoglobin < 8 g/dL.

Sample size was calculated a priori to be 120 subjects (60 subjects per arm) [30]. The primary endpoint used for sample size calculation was clinical effectiveness (therapeutic cure). Based on the meta-analysis of Ye et al., we assumed 85% cure rates in the peak–trough-based vancomycin TDM arm versus 60% cure rates in the control arm [31]. An attrition rate of 20%, a significance level of 5%, and a power of 80% were considered in the a priori power analysis [30]. Given the unexpectedly slow recruitment rate, interim analysis was conducted at 7 months. Statistically significant differences in the primary study outcome of clinical effectiveness were achieved. Thus, the study was ended after the enrollment of 65 subjects since a significant difference was detected in the primary study outcome.

2.3 Randomization and Blinding

Participants who provided informed consent and fulfilled the eligibility criteria were randomly assigned to one of the two study groups—(1) peak–trough (intervention) group or (2) trough-only (control) group. An allocation ratio of 1:1 was applied using a computer-generated list of random numbers. Due to the pragmatic nature of this trial, blinding was not possible since the treating clinical team needed to apply the dose change recommendations after justification. Thus, the method used for dose adjustment was revealed as part of justification, when requested by the attending physician.

2.4 Study Interventions

All subjects were initiated on vancomycin initial/empiric doses by the attending physician prior to enrollment in the study [3, 32–35]. Initiation or discontinuation of vancomycin treatment was the sole decision of the treating primary team and was not influenced by the study investigators. This trial was pragmatic in nature; thus, subjects were treated as part of routine care. No co-medications, medical procedures, dietary restrictions or restrictions to participation in other concurrent research were applied.

In the two study arms, target $C_{trough,ss}$ was as per the recommendations of the HMC institutional guidelines and the clinical practice guidelines: > 10 mg/L for less serious infections such as skin and soft tissue infections (SSTIs); and 15–20 mg/L for complicated infections such as bacteremia, infective endocarditis, osteomyelitis, meningitis, hospital-acquired pneumonia, and serious SSTI (e.g., necrotizing fasciitis) caused by *S. aureus* [3]. Creatinine clearance (CL_{CR}) was calculated using the Cockcroft–Gault equation [36]. In patients with declined renal function or at risk of nephrotoxicity, the lower end $C_{trough,ss}$ targets were used. In the intervention arm, target $C_{max,ss}$ was 20–40 mg/L [1], stratified according to the patient's renal function. In patients with normal CL_{CR}, $C_{max,ss}$ ≥ 30–35 mg/L was targeted. Otherwise, a lower $C_{max,ss}$ was used, considering clinical judgment and dosing feasibility. This range was used with the objective of sufficient infected tissue penetration while preventing adverse drug reactions (ADRs), by accounting for possible declined renal function and other nephrotoxicity risk factors [1].

2.4.1 Blood Specimen Collection for Initial Vancomycin Concentrations

In both study arms, five initial vancomycin blood samples were collected through venipuncture. Routine vancomycin trough concentrations were collected 30 min before the fourth dose ($C_{trough,ss1}$). For the study purpose, four vancomycin blood samples (10 mL of blood for each) were obtained at 1–2 h post fourth dose infusion ($C_{max,ss}$), 30 min before the fifth dose ($C_{trough,ss2}$), and two concentrations in between the peak and trough concentrations (C_1, C_2) after the fourth dose (i.e., at steady state). For instance, if the patient was receiving a 12-hourly vancomycin regimen, C_1 and C_2 were drawn at 4 h and 8 h post fourth dose infusion. On the other hand, if the patient was taking an 8-hourly regimen, C_1 and C_2 were drawn at 4 h and 6 h post fourth dose infusion.

2.4.2 Biochemistry and Microbiology Specimen Analysis

Vancomycin blood specimens were collected and analyzed at HMC biochemistry laboratories using particle-enhanced turbidimetric inhibition immunoassay (PETINA) [37]. Specimens from HGH and AKH were analyzed using the Architect c16000 (Abbott, USA) analyzer [38], while specimens from AWH were analyzed using the UniCel® DxC 600 (Beckman Coulter, USA) analyzer [39]. To determine vancomycin susceptibilities, microbiology cultures were processed using the broth microdilution test technique (BD Phoenix AP, USA) [40, 41]. Our institution uses the vancomycin MRSA susceptibly breakpoint (≤ 2 mg/L) set out by the Clinical and Laboratory Standards Institute (CLSI). For definitive sensitive cultures, the institutional laboratories reported MICs as '< 1 mg/L' or '= 1 mg/L'. A survey of institutional vancomycin MIC of sensitive MRSA isolates collected between April 2015 and January 2016 showed that the MICs for most cultures were reported as 1 mg/L. Thus, we assumed an MIC of 1 mg/L for all specimens in this study.

2.4.3 Trough-Only-Based Vancomycin Dosing Adjustment

In the control arm, only trough concentrations were considered for dosing adjustments. If the target trough was not achieved, a new dose or a new dosing interval was calculated using trough-only linear method equations (Eqs. 1, 2) as below [1, 42, 43], where $C_{\text{trough,ss}}$ is the target new steady-state trough concentration; C_t is the current trough concentration; D_{old} is the old dose that resulted in C_t; τ_{old} is the old dosing interval that resulted in C_t; and τ_{new} is the new dosing interval. Either the 'dose-only change' or the 'dosing interval-only' change equation was used based on clinical feasibility and practicality.

Dose-only change:

$$\text{New dose} = \left(C_{\text{trough,ss}}/C_t\right)D_{\text{old}} \tag{1}$$

Dosing interval-only change:

$$\text{New dosing interval } (\tau_{\text{new}}) = \left(C_t/C_{\text{trough,ss}}\right)\tau_{\text{old}} \tag{2}$$

2.4.4 Peak–Trough-Based Vancomycin Dosing Adjustment

Based on both the peak and trough vancomycin concentrations, a patient's individualized pharmacokinetic parameters were calculated and used in dose adjustment calculations. If either the peak or trough or both concentrations were non-therapeutic, a new vancomycin dosing regimen was calculated and administered. Intravenous (IV) bolus equations (Eqs. 3–7) were used provided that the vancomycin infusion time was short relative to the patient-specific vancomycin half-life [1, 42]. If this assumption was not valid due to augmented renal clearance (ARC) or infusion durations > 1 h, IV intermittent infusion equations (Eqs. 8–13) were used as below [1, 42]; where K_e is the elimination rate constant; k_0 is the infusion rate; $t_{1/2}$ is the half-life; V is the volume of distribution; Cl is the clearance; D is the dose; C_1 is the vancomycin concentration at time t_1; C_2 is the vancomycin concentration at time t_2; C_p is the peak concentration; C_t is the trough concentration; $C_{\text{max,ss}}$ is the target steady-state peak concentration; $C_{\text{trough,ss}}$ is the target steady-state trough concentration; τ is the dosing interval; and t' is the infusion duration.

IV bolus infusion equations:

$$K_e = -\left(\ln C_1 - \ln C_2\right)/\left(t_1 - t_2\right) \tag{3}$$

$$t_{1/2} = \ln 2/K_e \tag{4}$$

$$V = D/C_p - C_t \tag{5}$$

$$\tau = \left(\ln C_{\text{max,ss}} - \ln C_{\text{trough,ss}}\right)/k_e \tag{6}$$

$$\text{Dose} = C_{\text{max,ss}}V\left(1 - e^{-\text{ke}\,\tau}\right) \tag{7}$$

IV intermittent infusion equations:

$$K_e = -\left(\ln C_1 - \ln C_2\right)/\left(t_1 - t_2\right) \tag{8}$$

$$t_{1/2} = \ln 2/K_e \tag{9}$$

$$V = \left[k_0\left(1 - e^{-\text{ket}\prime}\right)\right]/\left\{k_e\left[C_p - \left(C_t e^{-\text{ket}\prime}\right)\right]\right\} \tag{10}$$

$$\text{Cl} = K_e V \tag{11}$$

$$\tau = \left(\ln C_{\text{max,ss}} - \ln C_{\text{trough,ss}}\right)/k_e + t' \tag{12}$$

$$\text{Dose} = C_{\text{max,ss}}K_e V\left[\left(1 - e^{-\text{ke}\,\tau}\right)/\left(1 - e^{-\text{ket}\prime}\right)\right] \tag{13}$$

2.4.5 Post-Dose Adjustment Vancomycin Monitoring

After any dose adjustment, the time to new steady state was calculated and post-dose adjustment peak and trough vancomycin concentrations were measured. If measured vancomycin concentrations were not at target levels, additional dose adjustments were applied as discussed above. Otherwise, vancomycin peak and trough concentration monitoring continued every 24–48 h.

2.5 Study Endpoints

2.5.1 Primary Outcome Measures

The primary outcome measures of clinical effectiveness were (1) vancomycin AUC_{24}/MIC cure breakpoint; (2)

therapeutic cure (composite endpoint); and (3) therapeutic failure (composite endpoint). Therapeutic cure was defined as clinical cure and/or microbiologic cure [6, 44–46]. Clinical cure was defined as the absence of infection signs/symptoms without the need for additional antibiotic treatment. Microbiologic cure was defined as negative blood cultures at 5 days after vancomycin treatment initiation. Therapeutic failure included at least one of the following [6, 44–46]—clinical failure, microbiologic failure, premature discontinuation due to ADR or all-cause mortality. Clinical failure was defined as insufficient clinical response to initial vancomycin therapy necessitating antibiotic change. Microbiological failure was defined as a positive culture at ≥ 5 days after initiation of vancomycin treatment. Neutropenia was defined as absolute neutrophil counts < 1000/µL [47, 48]. Nephrotoxicity was defined as 'a minimum of two or three consecutive SCr increases (defined as an increase of 0.5 mg/dL or at least 50% increase from baseline) after several days of vancomycin therapy' [3]. All-cause mortality was defined as death from any cause during enrollment in the trial.

2.5.2 Secondary Outcome Measures

Secondary outcomes included (1) length of hospital stay (LOS); (2) number of dose adjustments required; (3) cumulative vancomycin doses received; and (4) duration of vancomycin treatment.

2.6 Statistical Analysis

Intention-to-treat analysis was applied. Descriptive and inferential statistics were conducted (SPSSv.23; IBM®, Armonk, NY, USA) to compare the differences in clinical outcomes between the intervention (i.e., peak–trough-based vancomycin TDM approach) and the control (i.e., trough-only-based vancomycin TDM approach) arms. Skewness test was applied to ensure normality of data (choice of parametric vs nonparametric tests). For comparison between the groups, Student's *t*-test, Mann–Whitney *U*-test or chi-squared test was used as appropriate. All comparisons were carried out using an a priori significance level of 0.05 (two-sided tests). AUCs were calculated using the nonlinear mixed-effects population pharmacokinetics modeling approach (NONMEM v.7.3, ICON, USA) [49]. Classification and regression tree (CART) analysis was conducted using SPSS v.23 (IBM®; Armonk). AUC_{24}/MIC, vancomycin cumulative doses, treatment duration, infected physiologic compartment, ethnicity, CL_{CR} and TDM approach were tested against clinical effectiveness. To assess the predictive accuracy of the generated models, misclassification risk estimates with standard error were used [50].

3 Results

3.1 Baseline Characteristics of the Study Participants

Sixty-five subjects were enrolled (35 in the trough-only-based vancomycin TDM group and 30 in the peak–trough-based vancomycin TDM group). Baseline characteristics were similar between the study groups and are summarized in Table 1. Central nervous system infections ($n = 15$, 23.1%), lower respiratory tract infections ($n = 16$, 24.6%) and sepsis or septic shock ($n = 11$, 16.9%) were the most frequently occurring infections. Vancomycin was initiated as a definitive treatment in more than half of the cases ($n = 35$, 53.3%). Of the identified bacteria ($n = 35$), MRSA ($n = 17$, 48.6%), MSSA ($n = 8$, 22.9%), *S. epidermidis* ($n = 5$, 14.3%) and *Enterococcus faecium* ($n = 4$, 11.4%) constituted the most frequent positive microbiologic cultures. Approximately half of the study participants were critically ill and hospitalized in critical care units ($n = 31$, 47.7%). Physician-prescribed initial vancomycin dosing regimens were comparable between the study groups.

3.2 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 [p value = 0.02; Table 2]. Compared to the control group (trough-only-based TDM group), the intervention group (peak–trough-based TDM group) required non-statistically significant shorter duration of vancomycin treatment and hospitalization by 0.5 days and 4.5 days, respectively [p value > 0.05; Table 2]. No statistically significant differences were observed for other safety endpoints between the two monitored groups [p value > 0.05; Table 2].

3.3 Clinical Pharmacokinetic Outcomes of Peak–Trough-Based Versus Trough-Only-Based Vancomycin TDM Approaches

Initial peak and trough vancomycin serum concentrations were not therapeutic in 30.2% ($n = 19$) and 80% ($n = 52$) of cases, respectively (Table 3). Individual vancomycin clinical pharmacokinetic parameters were comparable between the study groups (Table 3). Patients enrolled in the peak–trough-based group received TDM earlier than the trough-only-based group by 0.5 days [p value = 0.001]. Vancomycin dosing requirements significantly differed between the two vancomycin TDM approaches; compared

Table 1 Baseline characteristics of the study participants

Variable	Trough-monitoring group ($n=35$)	Peak–trough-monitoring group ($n=30$)
Age (years), mean ± SD	41.7 ± 19.56	42.4 ± 14.47
BMI (kg/m^2), median [IQR]	26.7 [5.2]	25.4 [7.8]
ABW (kg), median [IQR]	73.1 [23.6]	70 [19.3]
Height (cm), median [IQR]	169 [13]	168 [10.5]
Gender, *n* (%)		
Male	30 (85.7)	22 (73.3)
Female	5 (14.3)	8 (26.7)
Ethnicity, *n* (%)		
MENA	23 (65.7)	8 (26.7)
Asian (non-MENA)	11 (31.4)	20 (66.7)
African (non-MENA)	1 (2.9)	2 (6.7)
Hospitalization ward, *n* (%)		
Intensive care units[a]	13 (37.1)	18 (60)
Burns unit	2 (5.7)	0 (0)
Medical ward	11 (31.4)	9 (30)
Surgical/orthopedic ward	9 (25.7)	3 (10)
Diagnosis, *n* (%)		
CNS infection[b]	5 (15.3)	10 (33.3)
Bacteremia	4 (11.4)	2 (6.7)
Skin and soft tissue infection	4 (11.4)	4 (13.3)
Bone and joint infection	6 (17.1)	2 (6.7)
Sepsis/septic shock	5 (14.3)	6 (20)
Lower respiratory tract infection	7 (20)	5 (16.7)
Infective endocarditis	1 (2.9)	0 (0)
Intra-abdominal infection	3 (8.6)	1 (3.3)
Infected physiologic compartment, *n* (%)		
CNS compartment[b]	5 (14.3)	10 (33.3)
Blood compartment[c]	13 (37.1)	9 (30)
Lung compartment	7 (20)	5 (16.7)
Other tissues[d]	10 (28.6)	6 (20)
Vancomycin treatment type, *n* (%)		
Empiric	16 (45.7)	14 (46.7)
Definitive	19 (54.3)	16 (53.3)
Positive microbiologic cultures, *n* (%)		
MRSA	8 (42.1)	9 (56.3)
MSSA	5 (26.3)	3 (18.6)
S. epidermidis	4 (21.1)	1 (6.3)
S. constellatus	1 (5.3)	0 (0)
E. faecium	1 (5.3)	3 (18.8)
Pre-enrollment vancomycin treatment details		
Pre-enrollment days on vancomycin treatment, median [IQR]	2 [0.5]	1.5 [1]
Dose (mg/dose), median [1QR]	1000 [0]	1000 [0]
Dose (mg/kg/dose), median [IQR]	14.3 [5.6]	14.6 [3.7]
Total daily dose (mg/day), median [IQR]	2000 [1000]	2000 [125]
Total daily dose (mg/kg/day), median [IQR]	28.6 [16.5]	29.2 [7.4]
Cumulative doses received (mg), median [IQR]	4000 [1250]	5000 [2063]
Cumulative doses received (mg/kg), median [IQR]	59.4 [25.04]	66.8 [29.6]

Table 1 (continued)

Variable	Trough-monitoring group ($n=35$)	Peak–trough-monitoring group ($n=30$)
Laboratory parameters		
White blood cells ($\times 10^9$ IU/L), mean ± SD	13.36 ± 7.9	12.8 ± 6.02
Hemoglobin (g/dL), median [IQR]	11.53 [2.32]	11.7 [4.15]
Neutrophils ($\times 10^9$ IU/L), median [IQR]	8 [9.8]	8.2 [7.7]
SCr (μmol/L), median [IQR]	65 [36]	67 [30]
Concomitant antibiotics, *n* (%)	18 (51.4)	22 (55)
Beta-lactams	9 (25.7)	9 (30)
Carbapenems	10 (15.4)	11 (16.9)
Cephalosporins	9 (25.7)	12 (40)
Clindamycin	2 (5.7)	1 (3.3)
Linezolid	0 (0)	4 (13.3)
Rifampicin	1 (2.9)	1 (3.3)
Concomitant nephrotoxic agents, *n* (%)	12 (34.3)	12 (40)
Amphotericin B	0 (0)	2 (6.7)
NSAIDs	8 (22.9)	10 (33.3)
ACEI/ARBs	4 (11.1)	1 (3.3)
Loop/thiazide diuretics	4 (11.4)	6 (20)
Acyclovir	1 (2.9)	0 (0)
Comorbidities, *n* (%)		
Diabetes mellitus	6 (17.1)	8 (26.7)
Chronic kidney disease	1 (2.9)	2 (6.7)
Hypertension	7 (20)	11 (36.7)
Coronary vascular disease	2 (5.7)	4 (13.3)
Heart failure	1 (2.9)	2 (6.7)

BMI body mass index, *ABW* actual body weight, *MENA* Middle East and North Africa, *MRSA* methicillin-resistant *S. aureus, MSSA* methicillin-sensitive *S. aureus*

[a]Includes trauma, medical and surgical intensive care units

[b]Involves meningitis, encephalitis and ventriculitis

[c]Includes blood, intra-abdominal and cardiac infections

[d]Includes skin, soft tissue, bone and joint infections

Table 2 Clinical 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[a]
Vancomycin treatment efficacy outcomes, *n* (%)			
Therapeutic cure	17 (48.6)	23 (76.7)	0.020
Therapeutic failure	18 (51.4)	7 (23.3)	
Vancomycin treatment safety outcomes, *n* (%)			
Neutropenia	3 (8.6)	1 (3.3)	0.381
Nephrotoxicity	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 [min–max]	20 [6–117]	15.5 [4–68.9]	0.320
Total duration on vancomycin treatment (days), median [min–max]	7 [1–28]	6.5 [1–32]	0.319

[a]Chi-squared test or Mann–Whitney *U*-test

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 3; Fig. 1]. Despite the similar duration on vancomycin treatment between the study groups, the trough-only-based vancomycin TDM recipients received clinically significant higher median cumulative vancomycin doses by 6,522 mg [p value > 0.05; Table 3]. Patients who received trough-only-based vancomycin TDM required more dose adjustments to achieve target serum concentrations compared to the intervention group [p value > 0.05; Table 3]. Furthermore, the trough-only-based monitoring was associated with recommended vancomycin dosing regimens of relatively low dosing frequencies and large single doses, necessitating longer infusion durations that exceeded 1 h (Table 3). 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 for 94.1% versus 69% of the time, respectively [p value = 0.006; Table 3]. Interestingly, peak–trough-based vancomycin doses resulted in similar rates of therapeutic troughs and AUCs compared to trough-only-based vancomycin doses (Table 3).

3.4 Association Between Vancomycin AUC_{24}/MIC and Cure

CART identified CL_{CR} < 7.85 L/h, AUC_{24}/MIC, 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. Maintaining AUC_{24}/MIC between 565 and 1256 has been associated with cure. All subjects who achieved an AUC_{24}/MIC ≤ 1256 and received peak–trough-based vancomycin TDM achieved clinical success rates [100%, n = 19]. Maintenance of AUC_{24}/MIC > 565 was identified to be correlated with cure in trough-only-based TDM recipients [84.6%, n = 11]. No minimum AUC_{24}/MIC breakpoint was detected by CART in the peak–trough-based group. The predictive performance was high (88.6%) with low misclassification risks (11.4%), suggesting robustness.

4 Discussion

To our knowledge, this is the first pragmatic head-to-head RCT that (1) prospectively compared two routinely used vancomycin TDM approaches; (2) reported MENA-specific AUC_{24}/MIC targets; and (3) identified a maximum AUC_{24}/MIC threshold for clinical benefit. Studies have suggested that vancomycin TDM was associated with higher clinical success rates and less nephrotoxicity compared to non-TDM groups [31, 51]. To date, studies in this area compared vancomycin TDM recipients with non-TDM recipients, and were mostly based on observational research designs [31]. In addition, no studies reported MENA-specific AUC_{24}/MIC targets. The present pragmatic RCT aimed to address these questions.

Despite similar AUC_{24} exposures, peak–trough-based TDM was associated with higher cure rates compared to trough-only-based TDM. This unexpected finding can be interpreted in two ways. First, it questions whether AUC_{24}/MIC is the optimal vancomycin pharmacokinetic–pharmacodynamic target. Fukumori's group reported the area under the trough level as a novel pharmacokinetic–pharmacodynamic parameter that more strongly correlates with vancomycin clinical efficacy compared to AUC_{24} [52]. Second, it suggests that cure may be more associated with the extent of consistency, sustainability and fluctuations of vancomycin exposure during the course of therapy, rather than a total single exposure estimate. This notion serves as the basis for studies advocating the administration of vancomycin as continuous infusion, rather than intermittent infusion [53–55]. Compared to intermittent infusion, continuous infusion resulted in more consistent and sustained exposure at the infection site, despite similar AUCs [54]. Furthermore, continuous infusion achieved target concentrations faster and was associated with less serum fluctuations [55]. Collectively these studies align with the finding that a minimum cure breakpoint (AUC_{24}/MIC > 565) was only detected in the trough-only TDM arm, while peak–trough-based vancomycin dosing was not associated with a minimum threshold. This suggests that peak–trough-based vancomycin dosing, using the specified peak/trough targets, is associated with more sustained and consistent vancomycin exposure that resulted in achieving the minimum AUC_{24}/MIC threshold for cure at most times, unlike trough-only based dosing. Vancomycin continuous infusion is not feasible for all clinical settings or patient situations. For example, a patient may be on other vancomycin-incompatible intravenous therapy. Indeed, the peak–trough-based approach may serve as a more practical alternative to continuous infusion that needs to be explored in future studies.

Maintaining AUC_{24}/MIC between 565 and 1256 has been associated with cure. This breakpoint is higher than the minimum AUC_{24}/MIC cure breakpoints that ranged from 398 to 451 in seven observational cohort studies [19]. Additionally, this work is the first to identify a maximum AUC_{24}/MIC cure threshold that, if exceeded, no extra clinical benefit is likely as long as the CL_{CR} is < 130 mL/min. This concurs with the emerging concept of ARC (CL_{CR} > 120–150 mL/min), that is associated with decreased vancomycin exposure and negative clinical outcomes [56–60]. Although studies reported that targeting, higher AUC_{24}/MIC ratios was associated

Table 3 Clinical pharmacokinetic outcomes associated with 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[a]
Pharmacokinetic parameters at treatment initiation			
V_d (L), mean ± SD	48.5 ± 10.7	51.14 ± 9.96	0.311
K_e (h^{-1}), mean ± SD	0.094 ± 0.05	0.089 ± 0.051	0.702
Cl (L/h), mean ± SD	4.15 ± 2.22	4.24 ± 2.20	0.861
$t_{1/2}$ (h), median [IQR]	8.01 [11.12]	7.23 [9.75]	0.722
CrCl (L/h), median [IQR]	6.51 [3.44]	6.45 [3.12]	0.374
AUC per initial[b] dose (mg*h/L), median [IQR]	227 [195.6]	228 [273.01]	0.590
Initial[b] vancomycin serum concentrations (mg/L), median [IQR]			
Trough-1	9 [8.3]	8.4 [12.9]	0.732
Peak	25 [10]	27.9 [17.8]	0.863
Random-1	18.9 [9.4]	18 [18.1]	0.837
Random-2	11.9 [8.7]	11.1 [13.28]	0.638
Trough-2	10.6 [10.5]	8.9 [15.1]	0.844
Interpretation of initial[b] peak vancomycin concentrations, n (%)[d]			
Therapeutic	27 (77.1)	17 (60.7)	0.158
Non-therapeutic	8 (22.9)	11 (39.3)	
Interpretation of initial[b] vancomycin trough concentrations, n (%)			
Therapeutic	6 (17.1)	7 (23.3)	0.534
Non-therapeutic	29 (82.9)	23 (76.7)	
Minimum number of dose adjustments required to first therapeutic serum concentrations, median [min–max]	2 [1–5]	1 [1–3]	0.105
Overall vancomycin dosing requirements			
Single dose (mg/dose), mean ± SD	1385.71 ± 530.62	1015 ± 332.221	0.001
Single dose (mg/kg/dose), mean ± SD	19.03 ± 7.76	14.09 ± 5.68	0.005
Total daily dose (mg/day), mean ± SD	3834.49 ± 1,362.83	2907 ± 1,416.08	0.009
Total daily dose (mg/kg/day), mean ± SD	52.83 ± 21.59	40.78 ± 21.25	0.027
Cumulative doses received (mg), mean ± SD	26,275 ± 24,190	19,753 ± 21,893	0.192
Vancomycin dosing interval, n (%)			
Q6 h	6 (17.1)	11 (36.7)	0.091
Q8 h	16 (45.7)	12 (40)	
Q12 h	13 (37.1)	4 (13.4)	
Q18 h	0 (0)	1 (3.3)	
Q24 h	0 (0)	1 (3.3)	
Q36 h	0 (0)	1 (3.3)	
Vancomycin infusion duration, n (%)			
Infused over 0.5 h	1 (2.9)	0 (0)	0.297
Infused over 1 h	19 (54.3)	22 (73.3)	
Infused over 1.5 h	10 (28.5)	8 (26.7)	
Infused over 2.5 h	2 (5.7)	0 (0)	
Infused over 3 h	2 (5.7)	0 (0)	
Infused over 4 h	1 (2.9)	0 (0)	
AUC per TDM adjusted dose(mg*h/L), median [IQR]	270 [156.02]	223 [168.82]	0.590
AUC_{24}/MIC, median [IQR]	772 [412.95]	708 [260.87]	0.762
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 3 (continued)

Variable	Trough-only-monitoring group ($n=35$)	Peak–trough-monitoring group ($n=30$)	p value[a]
Interpretation of post-dose adjustment[c] peak concentrations, n (%)[d]			
Therapeutic	29 (69)	32 (94.1)	0.006
Subtherapeutic	13 (31)	2 (5.9)	
Interpretation of post-dose adjustment[c] trough concentrations, n (%)			
Therapeutic	25 (44.6)	20 (54.1)	0.665
Subtherapeutic	19 (33.9)	10 (27)	
Supratherapeutic	12 (21.4)	7 (18.9)	

[a]Chi-squared test, Mann–Whitney *U*-test or Student's *t*-test

[b]Initial represents pre-TDM doses and concentrations

[c]56 dose adjustments were applied in the trough-only arm while 37 dose adjustments were applied in the peak–trough arm

[d]Missing values

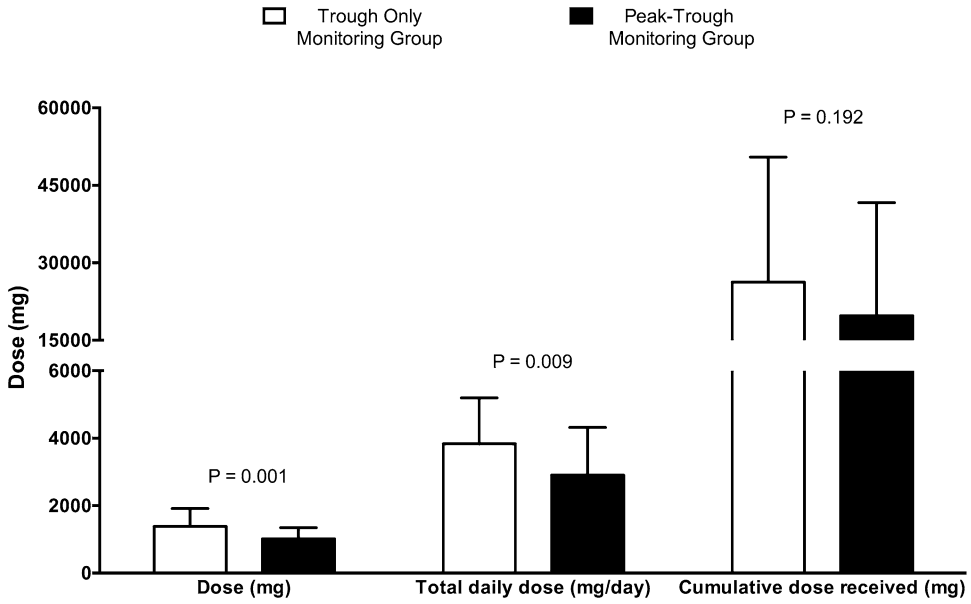

Fig. 1 Vancomycin dosing requirements of peak–trough-based versus trough-only-based vancomycin therapeutic drug monitoring recipients

with better clinical outcomes [19, 61], the question regarding a maximum AUC_{24}/MIC for clinical benefit remained unanswered in the current literature. It should be carefully noted that pharmacokinetic–pharmacodynamic targets (i.e., AUC_{24}/MIC) serve only for clinical efficacy outcomes while absolute vancomycin exposure measures should be monitored for safety [1, 3, 62, 63].

Emerging evidence suggests the promising clinical usefulness of the peak–trough-based vancomycin TDM approach [22, 64, 65], and questions the clinical benefit of trough-only-based vancomycin dosing [61, 66, 67]. Consistent with other studies, this RCT suggests that peak–trough-based vancomycin dosing may be associated with lower vancomycin exposure, LOS and dose adjustments, which needs to be confirmed in larger scale trials. Finch et al. reported that 2-concentration-based AUC-guided vancomycin dosing resulted in less vancomycin exposure, total daily doses and nephrotoxicity versus trough-only-guided dosing [22]. Similar clinical benefits of vancomycin peak concentration monitoring have been suggested elsewhere [64, 65]. Peak–trough-based TDM allowed significantly better attainment of therapeutic vancomycin concentrations [64]. It has been reported that vancomycin-related ADRs (i.e., nephrotoxicity and neutropenia) may be related to exposure [23, 47, 48, 68–72], with trough concentrations > 15 mg/L having a significantly higher risk [69]. According to a meta-analysis of 17 observational studies, vancomycin dosing that targeted higher trough concentrations (> 15 mg/L) was associated with significantly more nephrotoxicity and no significant improvement in mortality or cure rates [66]. In deep-seated

MRSA, trough concentrations > 15 mg/L did not result in shorter LOS, lower mortality rates, or higher treatment success rates versus trough concentrations < 15 mg/L [67]. In fact, vancomycin trough concentrations > 15 mg/L were associated with a higher incidence of nephrotoxicity [67]. A meta-analysis of 14 observational studies showed that vancomycin dosing based on trough concentration targets (15–20 mg/L) was not associated with better clinical outcomes in mortality, bacteremia persistence and treatment failure [61]. Therefore, peak–trough-based vancomycin dosing provides a potential strategy to decrease vancomycin exposure, which will reflect into lower medication utilization, less vancomycin-related ADRs, and decreased emergence of vancomycin-resistant strains. Furthermore, the possibly lower LOS with peak–trough-based dosing would potentially result in a lower incidence 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.

This study has several strengths. First, the present RCT is of a pragmatic nature. 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 [73]. Due to the limited generalizability of exploratory RCTs to routine clinical practice, the concept of pragmatism has emerged during the past decades [73–75]. Exploratory RCTs are conducted under ideal circumstances in 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 [73]. Therefore, it has been reported that the plethora of exploratory RCTs are of limited use to healthcare policymakers and clinicians [75]. Due to the pragmatic nature of this study, the researchers did not intervene on indication appropriateness and initial dosing of vancomycin; suspected or confirmed 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 in order to be reflective of the variabilities in clinical practice. An important observation is the lack of initial vancomycin target attainment with physician-initiated dosing at most times, which may be due to deviations from the guideline-recommended empiric doses in our clinical setting. The reasons for such non-compliance need to be explored in future audits. In addition, no restrictions on infection type, critical illness state, pharmacotherapeutic or mechanical co-interventions were applied. 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 assures the internal validity of clinical pharmacokinetic studies. Unlike most clinical evaluations that estimated the AUC based on estimated renal clearance, which does not accurately predict vancomycin clearance [23], 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 present findings need to be interpreted with caution due to some important limitations. This RCT was of limited sample size and was unblinded. The exact MICs were not available for all subjects since many received vancomycin as empiric therapy. For subjects with confirmed sensitive cultures, HMC laboratories reported MIC as 1 mg/L at all instances with values of < 1 mg/L rounded to 1 mg/L. Future larger scale double-blinded pragmatic RCTs are needed to confirm these findings.

5 Conclusion

In conclusion, this is the first head-to-head pragmatic RCT that compared peak–trough-based versus trough-only-based vancomycin TDM approaches. Compared to trough-only-based vancomycin TDM, peak–trough-based vancomycin TDM strategy was associated with higher cure rates and less vancomycin doses. Furthermore, maintaining an AUC_{24}/MIC between 565 and 1256 was associated with cure. Future larger scale trials are warranted to confirm these study findings.

6 Ethical Considerations

Informed consent was obtained from all participants included in the study. All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments and national institutional research committees. This study was approved by HMC Medical Research Center and Qatar University Institutional Review Board as well as the research committees of AWH, AKH and HGH.

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Compliance with Ethical Standards

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Conflicts of interest All authors declare no conflict of interest.

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