# Individualization of drug clearance predictions and dose regimens in patients with obesity using pharmacometric approaches

Zhang, T.

# 4

# How to dose vancomycin in overweight and obese patients with varying renal (dys)function in the novel era of AUC 400-600 mg·h/L-targeted dosing

This chapter is based on *Zhang T, et al. How to dose vancomycin in overweight and obese patients with varying renal (dys)function in the novel era of AUC 400-600 mg·h/L-targeted dosing. Clin Pharmacokinet. 2023 Nov 16.*

# ABSTRACT

**Background and Objective**

The latest vancomycin guideline recommends area under the curve (AUC)-targeted dosing and monitoring for efcacy and safety. However, guidelines for AUC-targeted starting dosing in patients with obesity and/or renal insufciency are currently lacking. This study quantifes the pharmacokinetics (PK) of vancomycin in this population and provides AUC-targeted dosing recommendations.

**Methods**

Vancomycin concentrations ($n$ = 1188) from therapeutic drug monitoring of 210 overweight and obese patients with varying degrees of renal (dys)function from the ward (74.8%) and intensive care unit (ICU, 25.2%) were pooled with published rich concentration-time data ($n$ = 207) from 20 (morbidly) obese subjects undergoing bariatric surgery. A population model was developed using NONMEM 7.4. Stochastic simulations were performed to design dosing guidelines targeting an $AUC_{24}$ between 400~600 mg·h/L.

**Results**

Vancomycin clearance ($CL$) was found to increase linearly with total bodyweight and with renal function (CKD-EPI) in a power relation. Additionally, $CL$ proved 15.5% lower in ICU patients. Our model shows that, to reach the target AUC between 400 and 600 mg·h/L in the first 48 h, two loading doses are required for both continuous infusion and intermittent dosing regimens. Maintenance doses were found to require adjustment for total bodyweight, renal function, and ICU admission status. With this guideline, the median $AUC_{24}$ is well within the target from the start of the treatment onwards.

**Conclusions**

To achieve safe and effective vancomycin exposure for maintenance doses in overweight and obese patients, renal function, total bodyweight, and ICU admission status should be taken into account.

## 4.1 Introduction

Obesity is a global epidemic, with a prevalence nearly tripling over the last five decades [1]. The World Health Organization (WHO) reported that approximately 39% of the global adult population are overweight [body mass index (BMI) ≥ 25 kg/m$^2$] and about 13% are obese (BMI ≥ 30 kg/m$^2$) [2]. Increasing numbers of patients with obesity with or without renal insufficiency are admitted to the hospital or develop renal insufficiency during hospital stay. These patients run the risk of getting severe bacterial infections for which antibiotic therapy is required.



Vancomycin is frequently used to treat severe infections caused by Gram-positive bacteria [e.g., *methicillin-resistant Staphylococcus aureus* (MRSA)]. For patients receiving vancomycin therapy, therapeutic drug monitoring (TDM) based on trough concentration was until recently commonly used as a surrogate target for the ratio of area under the curve over 24 h and minimal inhibitory concentration ($AUC_{24}$/MIC) [3]. However, the latest consensus guideline of vancomycin, published in 2020, recommends using the direct target of $AUC_{24}$ of 400~600 mg·h/L (assuming a MIC of 1 mg/L) to ensure clinical efficacy and minimize toxicity for various infections [4]. This revision is based on the evidence that the trough concentration is insufficient to predict AUC in at least 25% of cases, resulting in an overestimation of the required dose and a corresponding rise in vancomycin exposure for patients [5]. In addition, evidence also reveals that the AUC-targeted monitoring method is associated with significantly less vancomycin-induced acute kidney injury than a trough concentration-based approach. [6]

The new guideline also strongly recommends AUC-targeted dosing and monitoring in patients with obesity, renal insufficiency, or critical illness, since these conditions may significantly alter vancomycin clearance (*CL*) and increase the risk of nephrotoxicity if the dosage is not modified [4]. A recent prospective study of obese individuals weighing up to 235 kg and without renal insufficiency from our group quantified the increase of vancomycin *CL* with bodyweight, confirming reports of other studies showing vancomycin clearance increases with bodyweight [7 – 10]. However, this study did not consider overweight and obese individuals with renal dysfunction, who may have lower *CL* than those without renal dysfunction. To propose starting doses leading to target AUC and reduce the need for TDM-based dosage adjustments, quan-

tification of vancomycin pharmacokinetics (PK) in patients who are overweight or obese with varying levels of renal (dys)function is urgently needed.

This study uses population PK modeling to quantify the PK of vancomycin in a representative clinical population of overweight and (morbidly) obese patients with varying degrees of renal (dys)function. Using the developed model, AUC-targeted dosing recommendations are designed to obtain effective and safe vancomycin exposures from treatment initiation onward.



## 4.2 Patients and methods

### 4.2.1 Patients and data

Model building was based on the data from two datasets. The first dataset (patient dataset) contained retrospective PK data and patient characteristics extracted from electronic health records of St. Antonius Hospital in the Netherlands. Patients were included in this analysis when they **1)** were overweight or obese (BMI ≥ 25 kg/m$^2$), **2)** received vancomycin as a continuous infusion or intermittent dosing and had at least one vancomycin plasma concentration measurement within 168 h after the last dose, and **3)** had regular serum creatinine measurements across vancomycin treatment. Patients could be admitted to the ward or ICU and were excluded if they received renal replacement therapy during vancomycin treatment. Vancomycin was administered according to protocols for routine clinical practice, including TDM-based initial dosage and dose adjustments. The second dataset (healthy obese dataset) was obtained from the AMIGO trial, a prospective PK study that has been published previously [7]. Data from 20 (morbidly) obese (BMI ≥ 35 kg/m$^2$) subjects undergoing bariatric surgery were included in the analysis. All individuals had normal renal function defined as an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m$^2$. Subjects from this study were all dosed with 12.5 mg/kg vancomycin (maximum 2500 mg) by single intravenous infusion. Rich sampling was performed, yielding a median number of 11 samples per individual within 24 h after infusion.

In both datasets, vancomycin concentrations were measured with a validated and commercially available immune assay (VANC3) using Cobas platforms (Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of quantification was 4 mg/L

and the upper limit of quantification was 80 mg/L. The coefficient of variation was ≤ 4.4.

### 4.2.2 Ethics

For the first TDM dataset that was obtained during routine clinical care in the hospital, the Institutional Review Board (IRB) approved the protocol and waived the requirement of informed consent. The second dataset was part of the AMIGO trial, which was approved by the local human research and ethics committee (registered in the Dutch Trial Registry [NTR6058]) and all participants provided informed consent. All studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines in Good Clinical Practice.



### 4.2.3 Population pharmacokinetic analysis

A population PK analysis was performed using NONMEM 7.4 (ICON Development Solutions, Hanover, MD, USA). Pearl-speaks-NONMEM (PSN) 4.9.0 [11], Pirana 2.9.7 (Certara USA, Inc, Princeton, USA) [12], and R 4.0.3 (Xpose4 package 4.7.1) were used to organize, evaluate, and visualize data. ADVAN11 TRANS4 subroutine with the first-order conditional estimation method with interaction was used.

The structural model was selected from one-, two-, and three-compartment candidate models. Inter-individual variability on the parameters was assumed to follow a log-normal distribution and tested for statistical significance on each parameter. Inter-occasion variability ($IOV$) was investigated. Additive, proportional, and combined error models were tested to describe residual unexplained variability. For model selection, a drop in objective function value ($OFV$, −2 log-likelihood) of more than 3.84 was considered statistically significant ($p < 0.05$, assuming a $\chi^2$ distribution).

Covariates that were considered in the analysis were age, sex, bodyweight-related descriptors (including total bodyweight [TBW], lean bodyweight [LBW], adjusted bodyweight [ABW], ideal bodyweight [IBW], and BMI), and renal function estimates (quantified using Cockcroft-Gault calculated with LBW [CG-LBW] or TBW [CG-TBW], modification of diet in renal disease [MDRD], or chronic kidney disease epidemiology collaboration [CKD-EPI]). MDRD and CKD-EPI de-indexed for body surface area

(BSA) were also tested. The equations for calculating bodyweight descriptors and renal function can be found in **Supplementary Table S4.1**. ICU admission status, indicating whether a patient was admitted to ICU, was also explored as a covariate. Potential covariates were implemented into the model separately using a linear function or a power function with an estimated exponent. A covariate relationship was considered statistically significant when $OFV$ dropped more than 10.83 ($p < 0.001$). The model fits were assessed using goodness-of-fit (GOF) plots stratified for the BMI group (overweight [BMI 25~30 kg/m$^2$] and obese [BMI > 30 kg/m$^2$]), stratified for the estimated renal function group (CKD-EPI < 30, 30~50, 50~90, > 90 mL/min/1.73 m$^2$) and ICU admission status. Plots of individual influence on change in $OFV$ (also known as shark plots) in Xpose 4 were used to ascertain that statistical significance was driven by a sufficient number of individuals and it was checked that the inclusion of a covariate reduced the random inter-individual variability on a parameter [13]. In addition, covariate relationships were visually inspected in plots of eta value *versus* individual covariate value for time-independent covariates, conditional weighted residuals (CWRES) *versus* individual covariate value for time-dependent covariates, and individual *post hoc* parameter estimates *versus* covariate value overlain with lines representing the obtained covariate relationships, with the stratifications previously mentioned. Finally, relative standard errors of estimates (RSE) were considered to indicate adequate precision if they were below 50%.

### 4.2.4 Model evaluation

In addition to the diagnostic plots used during model development, the robustness of the parameter estimates of the final model was validated by a bootstrap resampling analysis using PsN [12], with 1000 replicates stratified on the two datasets.

The predictive performance of the final model was assessed and visualized by a normalized prediction distribution error (NPDE) analysis using the NPDE package in R [14]. The analysis was based on 1000 simulations of the dataset.

### 4.2.5 Model-based dose optimization

On the basis of the obtained covariate relationships in the final model and clinical feasibility, AUC-targeted dosing recommendations for continuous infusion and intermittent dosing regimen were developed, which were assessed in stochastic simulations using the final vancomycin PK model. For representative virtual individuals with assigned values of indexed CKD-EPI (20, 40, 60, 80, and 100 mL/min/1.73 $m^2$), bodyweight (80, 120, 160, and 200 kg), and ICU admission status (non-ICU *versus* ICU), 1000 simulations with inter-individual variability were performed. The target exposure for efficacy was defined as $AUC_{24}$/MIC ≥ 400 mg·h/L. An $AUC_{24}$/MIC threshold of 600 mg·h/L was selected as the safety limit to minimize the probability of nephrotoxicity according to the literature [15–17]. Since the MIC was assumed to be 1 mg/L in this study, $AUC_{24}$/MIC is abbreviated as $AUC_{24}$ for simplicity. Therefore, optimal dose regimens should achieve the target $AUC_{24}$ from the first day of dosing onward. To explore the concentrations that are obtained upon these $AUC_{24}$ 400~600 mg·h/L targeted dosing recommendations, concentration-time profiles for the different bodyweight and renal function groups were also explored.



## 4.3 Results

### 4.3.1 Data

A total of 1188 concentrations were available from 210 overweight and obese hospitalized patients, which were analyzed in conjunction with 207 concentrations from 20 morbidly obese healthy subjects. Of the 1188 concentrations, 11 were peak and 416 were trough concentrations taken upon intermittent infusion, while 761 were random samples taken upon the continuous infusion. A summary of baseline demographics, clinical characteristics, and dosing information from the study groups is presented in **Table 4.1**.

### 4.3.2 Population pharmacokinetic analysis

A three-compartment model outperformed both one- and two-compartment models, exhibiting the best GOF plots. This model, which incorporated inter-individual vari-

**Table 4.1** Baseline demographics, clinical characteristics, and dosing information from the overweight and obese patients and otherwise healthy obese subjects undergoing bariatric surgery included in the analysis

| Parameters | Overweight and obese patients | Otherwise healthy obese subjects [7] | Total dataset |
|---|---|---|---|
| Number of individuals | 210 | 20 | 230 |
| Male/Female | 133/77 | 7/13 | 140/90 |
| Height (m) | 1.73 (1.49~1.97) | 1.74 (1.59~1.90) | 1.72 (1.49~1.97) |
| Age (years) | 72 (33~92) | 39 (23~54) | 70 (23~92) |
| ICU/non-ICU | 53/157 | 0/20 | 53/177 |
| TBW (kg) | 90.1 (58.6~143.0) | 141.2 (110.6~234.6) | 91.8 (58.6~234.6) |
| LBW (kg) | 60.8 (36.5~85.4) | 65.1 (52.7~104.2) | 61.0 (36.5~104.2) |
| ABW (kg) | 76.1 (50.4~106.0) | 98.3 (75.1~143.7) | 77.0 (50.4~143.7) |
| BSA ($m^2$) | 2.1 (1.6~2.7) | 2.5 (2.1~3.3) | 2.1 (1.6~3.3) |
| BMI ($kg/m^2$) | 29.2 (25.0~53.4) | 45.3 (40.8~65.7) | 30.0 (25.0~65.7) |
| 25~30 (no. of patients) | 122 | 0 | 122 |
| > 30 (no. of patients) | 88 | 20 | 108 |
| Serum creatinine (μmol/L) | 84.0 (23.0~748.0) | 72.0 (41.0~101.0) | 84.0 (23.0~748.0) |
| No. of serum creatinine per individual | 11.0 (1.00~91.0) | 1 | 11.0 (1.00~91.0) |
| CKD-EPI (mL/min/1.73 $m^2$) | 73.7(6.0~154.9) | 100.3 (70.3~119.8) | 74.5 (6.0~154.9) |
| < 30 (no. of patients) | 15 | 0 | 15 |
| 30~60 (no. of patients) | 60 | 0 | 60 |
| 60~90 (no. of patients) | 87 | 6 | 93 |
| 90~130 (no. of patients) | 46 | 14 | 60 |
| > 130 (no. of patients) | 2 | 0 | 2 |
| De-indexed CKD-EPI (mL/min) | 86.6 (6.5~209.5) | 142.4 (95.5~221.8) | 87.8 (6.5~221.8) |
| MDRD (mL/min/1.73 $m^2$) | 71.5 (6.4~304.1) | 88.0 (61.9~145.5) | 72.6 (6.4~304.1) |
| De-indexed MDRD (mL/min) | 85.8 (6.9~371.0) | 128.7 (84.1~207.4) | 86.6 (6.9~371.0) |
| CG-TBW (mL/min) | 86.4 (9.6~420.6) | 208.9 (143.4~432.1) | 87.8 (9.6~432.1) |
| CG-LBW (mL/min) | 56.3 (6.9~280.7) | 107.0 (70.7~192.0) | 57.2 (6.9~280.7) |
| Vancomycin dose (mg) | 1250 (250~3500) | 690 (1400~2500) | 1250 (250~3500) |
| Vancomycin dose (mg/kg) | 13.6 (2.4~36.6) | 12.3 (10.7~13.6) | 13.6 (2.4~36.6) |
| Treatment duration (h)[a] | 134.2 (7.52~1407.8) | 13.1 (4.5~22.2)[b] | 112.8 (4.5~1407.8) |
| No. of concentrations | 1188 | 207 | 1395 |
| No. of concentrations per individual | 4 (1~31) | 11 (7~12) | 5 (1~31) |
| Time after the last dose (h) | 11.4 (0.02~44.6) | 4.7 (0.5~22.2) | 10.7 (0.02~44.6) |

Data are shown as median (range) unless specified otherwise

TBW total bodyweight, LBW lean bodyweight, ABW adjusted bodyweight, BSA body surface area, BMI body mass index, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration, MDRD renal function calculated by modification of diet in renal disease, CG-TBW renal function calculated by Cockcroft-Gault with TBW, CG-LBW renal function calculated by CG calculated with LBW For the equations of bodyweight descriptors and renal function, see **Supplementary Table S4.1**

[a] Time between the first dose and the last observation

[b] Single dose infusion

ability on $CL$ and central volume of distribution ($V1$), best described the data.

In the covariate analysis, indexed CKD-EPI gave the largest reduction in $OFV$ and was identified as the most predictive covariate on $CL$, with an estimated exponent in a power relationship of 0.658 ($p < 0.001$). TBW was identified as the second covariate on $CL$, as it was significantly correlated with vancomycin $CL$ in a linear function ($p < 0.001$) and found to be superior to the other tested size descriptors. Furthermore, ICU admission status was also significantly correlated with vancomycin $CL$ ($p < 0.001$), with $CL$ in ICU patients being 15.5% lower than in non-ICU patients. For the volume of distribution of the peripheral compartments and the inter-compartmental clearances, a statistically significant correlation with TBW was found ($p < 0.001$). However, since for each parameter only three individuals (1.30%) were found to contribute to yielding statistical significance, we decided not to include TBW as a covariate on the peripheral compartments and intercompartmental clearances. No other covariates were found to have a statistically significant impact on vancomycin PK in our population. The PK parameters of vancomycin for the final model are presented in **Table 4.2**.

In the final model, $CL$ was 3.36 L/h in a typical patient with a TBW of 100 kg and indexed CKD-EPI of 75 mL/ min/1.73 $m^2$. For a patient admitted to the ICU, this value was 2.84 L/h. The influences of renal function (CKD-EPI), bodyweight (TBW), and ICU admission status on $CL$ are illustrated in **Figure 4.1**.

### 4.3.3 Model evaluation

The GOF plots of the final model, stratified on renal function (CKD-EPI), bodyweight (TBW), and ICU admission status, are shown in **Supplementary Figure S4.1**. The figure shows that observed vancomycin concentrations are described without bias in all subpopulations, with the exception of the group with the worst kidney function (CKD-EPI < 30 mL/min/1.73 $m^2$) in which a small trend towards under-prediction can be seen.

The bootstrap analysis (presented in **Table 4.2**) confirmed the robustness of the parameter estimates in the final model. Bootstrapped median values generally deviated less than 10% from the original estimate and all originally estimated values were within the 95% confidence interval (CI) of the bootstrapped values.

**Table 4.2** Population pharmacokinetic parameter estimates of vancomycin for the final model for overweight and obese patients and otherwise healthy obese subjects, and results of bootstrap analysis

| Parameters | Final model (RSE%) | Bootstrap median [95% CI] |
|---|---|---|
| $CL(\text{L/h}) = TVCL \times (\frac{CKDEPI}{75})^{\theta 1} \times [1 + \theta 2 \times (TBW - 90)] \times F_{\text{ICU}}$ | | |
| $TVCL$ | 3.36 (2.60) | 3.35 (3.17~3.56) |
| $\theta 1$ | 0.658 (3.10) | 0.657 (0.526~0.773) |
| $\theta 2$ | 0.0106 (13.8) | 0.0105 (0.00806~0.0129) |
| $F_{\text{ICU}}$ [a] | 0.845[a] (2.30) | 0.841 (0.717~0.963)[a] |
| $V1$ (L) | 16.7 (14.0) | 16.8 (11.7~23.1) |
| $Q2$ (L/h) | 16.1 (11.5) | 16.0 (14.0~18.7) |
| $V2$ (L) | 23.1 (3.60) | 23.1 (19.7~25.8) |
| $Q3$ (L/h) | 2.44 (8.00) | 2.47 (1.90~3.91) |
| $V3$ (L) | 83.0 (4.50) | 83.2 (65.3~111.2) |
| **Inter-individual variability ($\omega^2$)** | | |
| $CL$ | 0.0730 (10.5) | 0.0730 (0.0503~0.104) |
| $V1$ | 0.978 (29.1) | 0.926 (0.428~1.48) |
| **Residual unexplained variability** | | |
| PA data: additive error (mg/L) | 9.32 (3.20) | 9.26 (7.98~10.9) |
| HS data: proportional error (−) | 0.00216 (41.2) | 0.00231 (0.000278~0.00571) |
| HS data: additive error (mg/L) | 1.10 (15.4) | 0.783 (0.119~2.30) |

$CL$ clearance, $V1$ volume of distribution of central compartment, $V2$ volume of distribution of peripheral compartment 2, $V3$ volume of distribution of peripheral compartment 3, $Q2$ inter-compartmental clearance between $V1$ and $V2$, $Q3$ inter-compartmental clearance between $V1$ and $V3$, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration equation (indexed, mL/min/1.73 $m^2$), TBW total bodyweight (kg), $F_{\text{ICU}}$ scaling factor to be used for ICU patients, PA patients (ICU and non-ICU), HS obese but otherwise healthy subjects undergoing bariatric surgery, RSE relative standard error, CI confidence interval

[a] The parameter is 1 in the case that the patient is not admitted to ICU

Visual inspection and statistical tests of the NPDE results based on 1000 simulation shows the final model have had a good predictive performance for subpopulations with different renal function, bodyweights, and ICU admission status (**Supplementary Figure S4.2**). The model is shown to accurately describe typical trends as well as the variability in the populations.

### 4.3.4 Model-based dose optimization

To achieve $AUC_{24}$ exposure of 400~600 mg·h/L in overweight and obese patients with varying degrees of renal function, dosing guidelines for continuous infusion and intermittent dosing regimens were developed. The regimens for the ward patients are

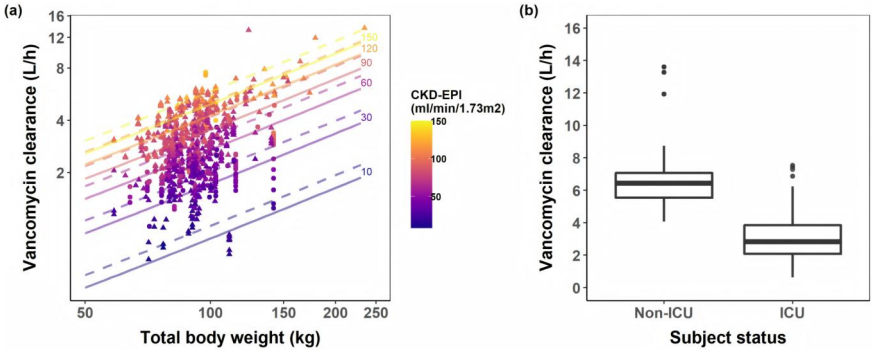
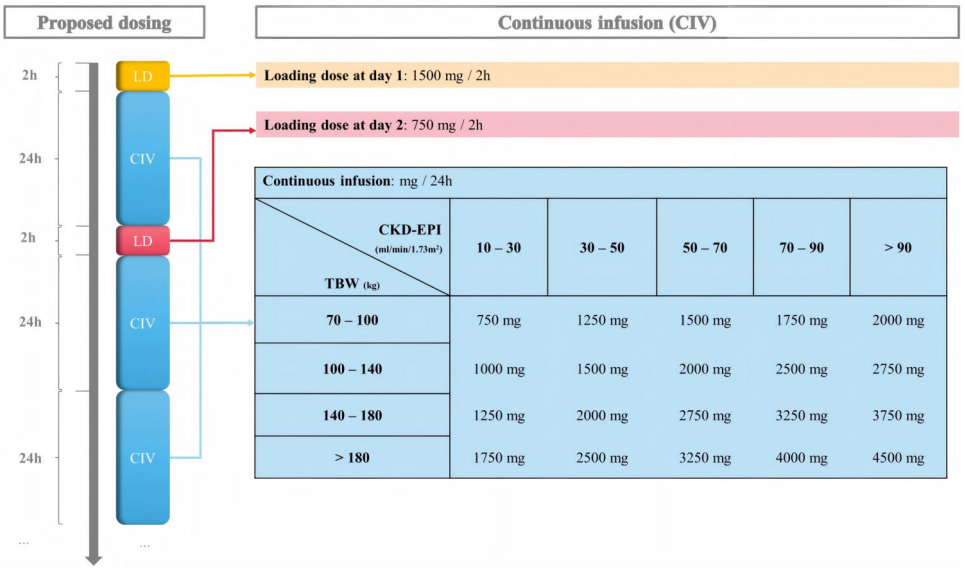



**Figure 4.1** Illustration of covariate effects on vancomycin clearance (*CL*) in overweight and obese individuals with varying renal function. **(a)** Individually predicted *CL* values *versus* bodyweight (symbols) and population-predicted *CL* values *versus* bodyweight (lines) (log scale for both *x*- and *y*-axes). Non-ICU subjects are indicated by triangles and dashed lines and ICU patients by circles and solid lines. The color of symbols and lines vary with renal function expressed as CKD-EPI as indicated in the legend. **(b)** The distributions of individually predicted *CL* values are shown as a boxplot for non-ICU and ICU patients ($p < 0.001$). The boxplot shows the median and interquartile ranges. Whiskers represent values from interquartile to maximum or minimum; values beyond the minimum or maximum are drawn as circles. CKD-EPI renal function calculated by the chronic kidney disease epidemiology collaboration equation. Note: The *y*-axes are different in **(a)** and **(b)**

shown in **Figures 4.2** and **4.3**, while those for the ICU patients are shown in **Figures 4.4** and **4.5**. These tables present that for both schemes, higher doses are needed with increasing bodyweight and renal function, and in non-ICU patients compared with ICU patients.

To obtain the vancomycin therapeutic exposure immediately at the start of the treatment, two loading dose administrations for both continuous infusion and intermittent dosing regimens were required. For continuous infusion, a loading dose of 1500 mg is given as a 2-h infusion before starting the maintenance infusion on day 1, and another loading dose of 750 mg is given over 2 h on day 2, after which the maintenance infusion is continued. In patients on an intermittent dosing, two loading doses given as a 2-h infusion at 12-h intervals are proposed on the first day of treatment. From the second day onwards, maintenance doses can be given one or two times per day depending on the patient renal function, bodyweight, and ICU admission status. More details of these dosing regimens can be found in **Figures 4.2**, **4.3**, **4.4** and **4.5**.

The obtained daily $AUC_{24}$ and concentration profiles in the first week of treatment for the defined representative virtual individuals with various combinations of the



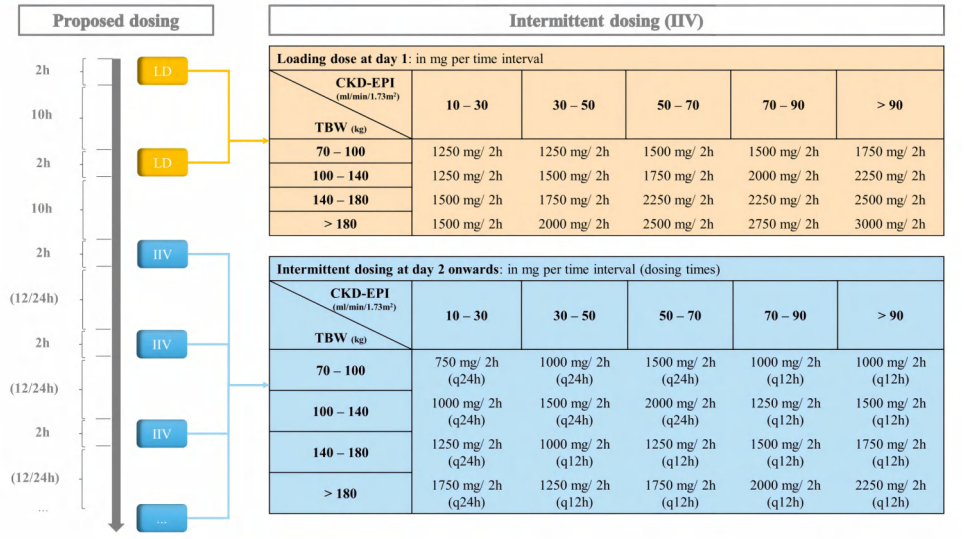

**Loading dose at day 1**: 1500 mg / 2h

**Loading dose at day 2**: 750 mg / 2h

**Continuous infusion**: mg / 24h

| TBW (kg) \ CKD-EPI (ml/min/1.73m²) | 10 – 30 | 30 – 50 | 50 – 70 | 70 – 90 | > 90 |
|---|---|---|---|---|---|
| 70 – 100 | 750 mg | 1250 mg | 1500 mg | 1750 mg | 2000 mg |
| 100 – 140 | 1000 mg | 1500 mg | 2000 mg | 2500 mg | 2750 mg |
| 140 – 180 | 1250 mg | 2000 mg | 2750 mg | 3250 mg | 3750 mg |
| > 180 | 1750 mg | 2500 mg | 3250 mg | 4000 mg | 4500 mg |

**Figure 4.2** Dosing guideline for vancomycin in overweight and obese patients (**non-ICU patients**) with varying renal function receiving continuous infusion. TBW total bodyweight, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration equation



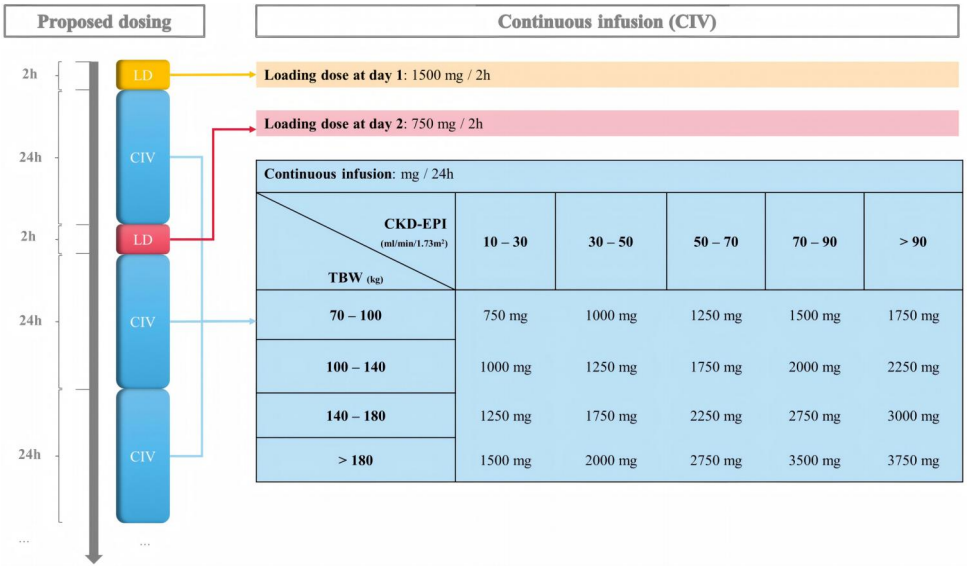

**Loading dose at day 1**: in mg per time interval

| TBW (kg) \ CKD-EPI (ml/min/1.73m²) | 10 – 30 | 30 – 50 | 50 – 70 | 70 – 90 | > 90 |
|---|---|---|---|---|---|
| 70 – 100 | 1250 mg/ 2h | 1250 mg/ 2h | 1500 mg/ 2h | 1500 mg/ 2h | 1750 mg/ 2h |
| 100 – 140 | 1250 mg/ 2h | 1500 mg/ 2h | 1750 mg/ 2h | 2000 mg/ 2h | 2250 mg/ 2h |
| 140 – 180 | 1500 mg/ 2h | 1750 mg/ 2h | 2250 mg/ 2h | 2250 mg/ 2h | 2500 mg/ 2h |
| > 180 | 1500 mg/ 2h | 2000 mg/ 2h | 2500 mg/ 2h | 2750 mg/ 2h | 3000 mg/ 2h |

**Intermittent dosing at day 2 onwards**: in mg per time interval (dosing times)

| TBW (kg) \ CKD-EPI (ml/min/1.73m²) | 10 – 30 | 30 – 50 | 50 – 70 | 70 – 90 | > 90 |
|---|---|---|---|---|---|
| 70 – 100 | 750 mg/ 2h (q24h) | 1000 mg/ 2h (q24h) | 1500 mg/ 2h (q24h) | 1000 mg/ 2h (q12h) | 1000 mg/ 2h (q12h) |
| 100 – 140 | 1000 mg/ 2h (q24h) | 1500 mg/ 2h (q24h) | 2000 mg/ 2h (q24h) | 1250 mg/ 2h (q12h) | 1500 mg/ 2h (q12h) |
| 140 – 180 | 1250 mg/ 2h (q24h) | 1000 mg/ 2h (q12h) | 1250 mg/ 2h (q12h) | 1500 mg/ 2h (q12h) | 1750 mg/ 2h (q12h) |
| > 180 | 1750 mg/ 2h (q24h) | 1250 mg/ 2h (q12h) | 1750 mg/ 2h (q12h) | 2000 mg/ 2h (q12h) | 2250 mg/ 2h (q12h) |

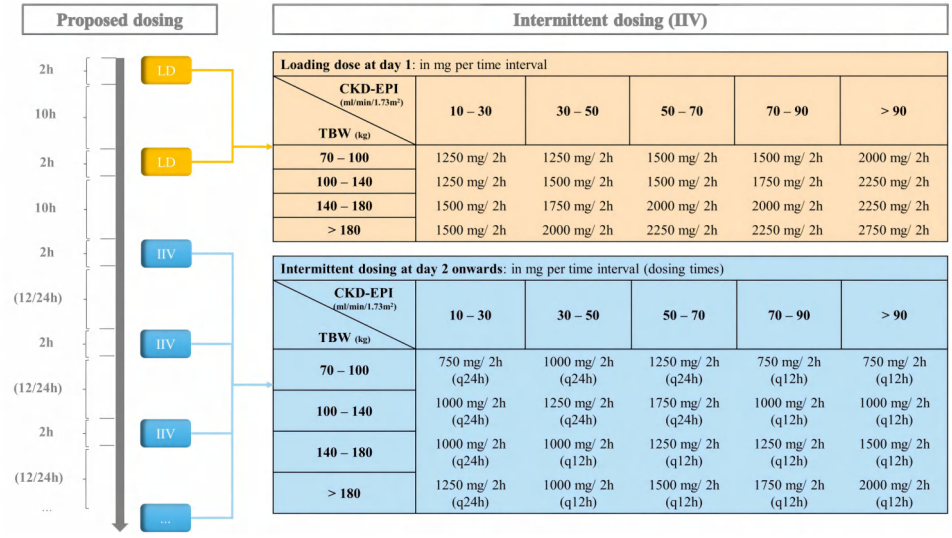
**Figure 4.3** Dosing guideline for vancomycin in overweight and obese patients (**non-ICU patients**) with varying renal function receiving intermittent dosing regimen. TBW total bodyweight, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration equation, q24h once daily, q12h twice daily




**Continuous infusion**: mg / 24h

| CKD-EPI (ml/min/1.73m²) / TBW (kg) | 10 – 30 | 30 – 50 | 50 – 70 | 70 – 90 | > 90 |
|---|---|---|---|---|---|
| 70 – 100 | 750 mg | 1000 mg | 1250 mg | 1500 mg | 1750 mg |
| 100 – 140 | 1000 mg | 1250 mg | 1750 mg | 2000 mg | 2250 mg |
| 140 – 180 | 1250 mg | 1750 mg | 2250 mg | 2750 mg | 3000 mg |
| > 180 | 1500 mg | 2000 mg | 2750 mg | 3500 mg | 3750 mg |

**Figure 4.4** Dosing guideline for vancomycin in overweight and obese patients (**ICU patients**) with varying renal function receiving continuous infusion. TBW total bodyweight, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration equation




**Loading dose at day 1**: in mg per time interval

| CKD-EPI (ml/min/1.73m²) / TBW (kg) | 10 – 30 | 30 – 50 | 50 – 70 | 70 – 90 | > 90 |
|---|---|---|---|---|---|
| 70 – 100 | 1250 mg/ 2h | 1250 mg/ 2h | 1500 mg/ 2h | 1500 mg/ 2h | 2000 mg/ 2h |
| 100 – 140 | 1250 mg/ 2h | 1500 mg/ 2h | 1500 mg/ 2h | 1750 mg/ 2h | 2250 mg/ 2h |
| 140 – 180 | 1500 mg/ 2h | 1750 mg/ 2h | 2000 mg/ 2h | 2000 mg/ 2h | 2250 mg/ 2h |
| > 180 | 1500 mg/ 2h | 2000 mg/ 2h | 2250 mg/ 2h | 2250 mg/ 2h | 2750 mg/ 2h |

**Intermittent dosing at day 2 onwards**: in mg per time interval (dosing times)

| CKD-EPI (ml/min/1.73m²) / TBW (kg) | 10 – 30 | 30 – 50 | 50 – 70 | 70 – 90 | > 90 |
|---|---|---|---|---|---|
| 70 – 100 | 750 mg/ 2h (q24h) | 1000 mg/ 2h (q24h) | 1250 mg/ 2h (q24h) | 750 mg/ 2h (q12h) | 750 mg/ 2h (q12h) |
| 100 – 140 | 1000 mg/ 2h (q24h) | 1250 mg/ 2h (q24h) | 1750 mg/ 2h (q24h) | 1000 mg/ 2h (q12h) | 1000 mg/ 2h (q12h) |
| 140 – 180 | 1000 mg/ 2h (q24h) | 1000 mg/ 2h (q12h) | 1250 mg/ 2h (q12h) | 1250 mg/ 2h (q12h) | 1500 mg/ 2h (q12h) |
| > 180 | 1250 mg/ 2h (q24h) | 1000 mg/ 2h (q12h) | 1500 mg/ 2h (q12h) | 1750 mg/ 2h (q12h) | 2000 mg/ 2h (q12h) |

**Figure 4.5** Dosing guideline for vancomycin in overweight and obese patients (**ICU patients**) with varying renal function receiving intermittent dosing regimen. TBW total bodyweight, CKD-EPI renal function calculated by chronic kidney disease epidemiology collaboration equation, q24h once daily, q12h twice daily

bodyweight and renal function are illustrated in **Figures 4.6 and 4.7**, for the ward patients and ICU patients, respectively. These figures indicate that when our proposed guidelines for either continuous infusion or intermittent dosing are applied, the median $AUC_{24}$ is within the target of 400~600 mg·h/L, regardless of renal function, bodyweight, and ICU admission status, even though for some ICU subgroups AUC may be slightly above 600 mg·h/L (**Figure 4.7**). However, even though the $AUC_{24}$ generally reaches the target, the concentrations that are obtained across the entire patient population are highly variable and often lower than previously used target concentrations. More specifically, median (interquartile range) values of (trough) concentration for continuous infusion and intermittent dosing are 23.08 (19.54~27.29) mg/L and 16.89 (12.65~20.50) mg/L, respectively. These figures also show that time to steady-state concentrations in obese patients, particularly in those with renal dysfunction admitted to the ICU, exceeds 5 days.

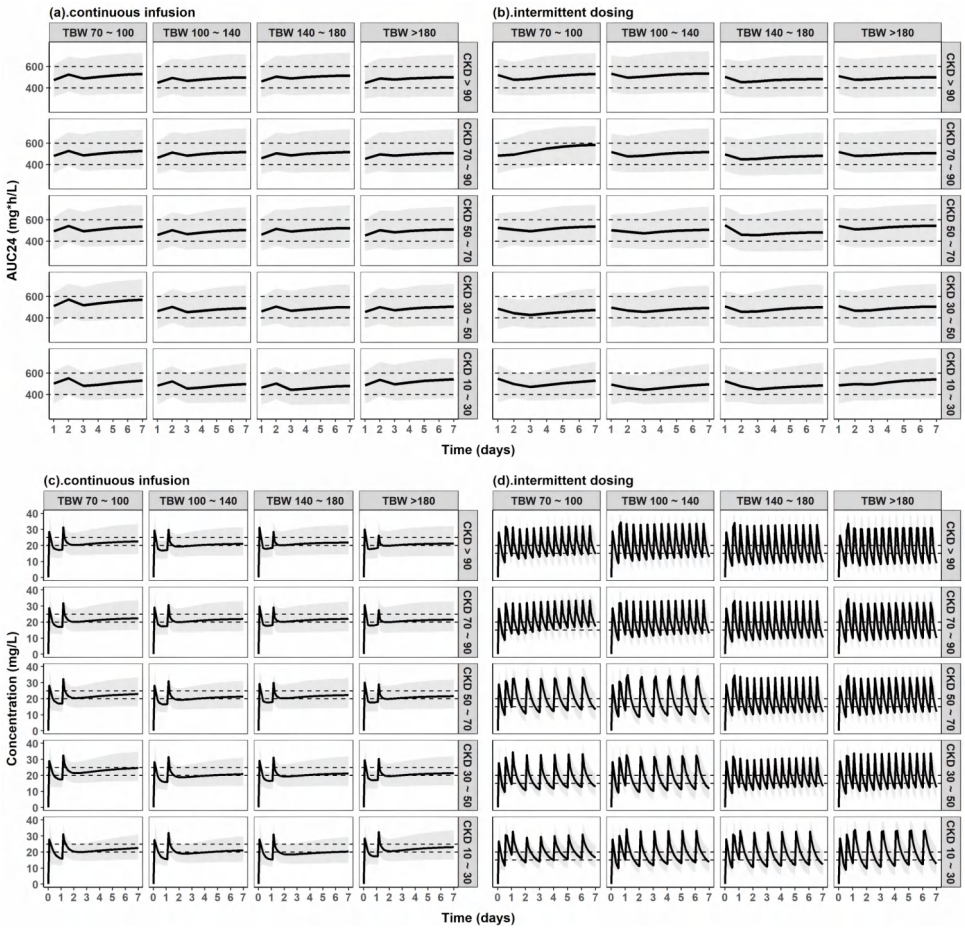



**Figure 4.6** Vancomycin 24-h area under the curve values ($AUC_{24}$) **(a, b)** and concentrations **(c, d)** in the 7 days of treatment for representative virtual individuals from four bodyweight groups with renal functions estimates of 100, 80, 60, 40 and 20 mL/min/1.73 $m^2$ (**non-ICU patients**) receiving continuous infusion **(a, c)** and intermittent dosing regimen **(b, d)** on the basis of our proposed dosing guideline (see **Figures 4.2, 4.3**). Dashed lines in the plots of $AUC_{24}$ **(a, b)** represent the targeted efficacy and safety range, while in the plots of concentration **(c, d)** represent the defined concentrations corresponding to therapeutic range of the $AUC_{24}$ according to the literature (20~25 mg/L for continuous infusion and 15~20 mg/L for intermittent dosing regimens). The shaded areas represent the 95% prediction interval of the predicted $AUC_{24}$ or concentration. CKD-EPI renal function calculated by the chronic kidney disease epidemiology collaboration equation in (mL/min/1.73 $m^2$), TBW total bodyweight in kg

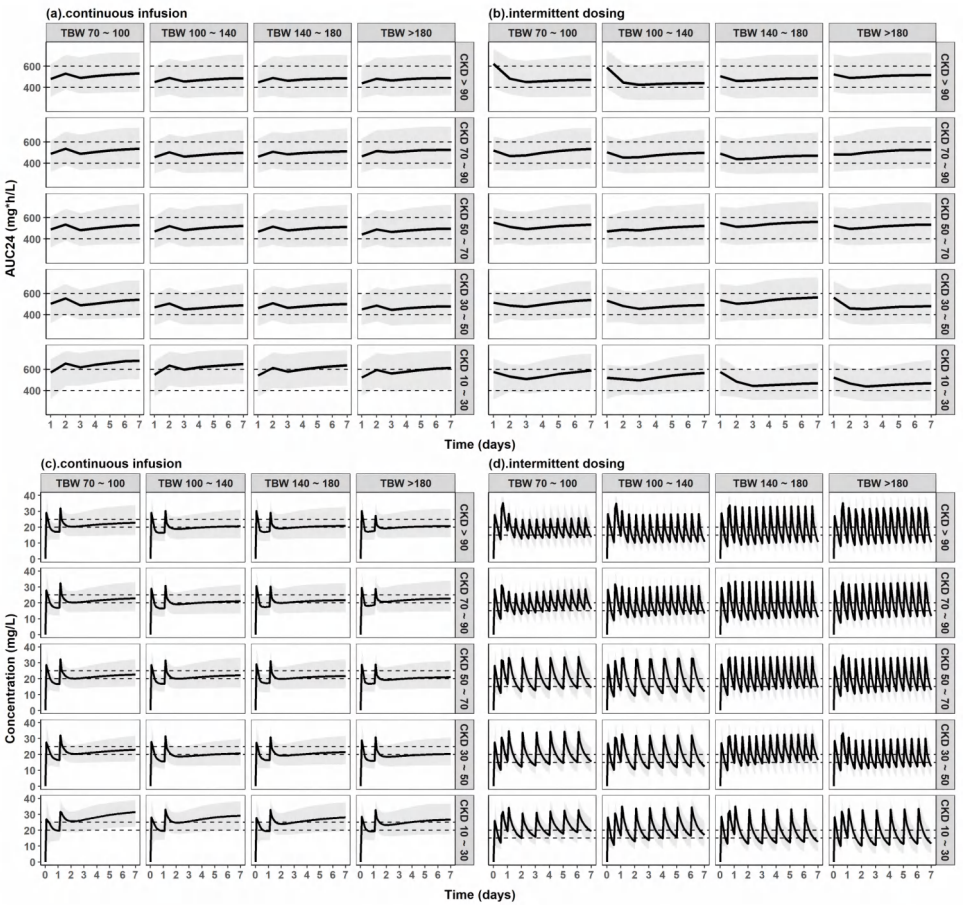



**Figure 4.7** Vancomycin 24-h area under the curve values ($AUC_{24}$) **(a, b)** and concentrations **(c, d)** in the 7 days of treatment for representative virtual individuals from four bodyweight groups with renal functions estimates of 100, 80, 60, 40 and 20 mL/min/1.73 $m^2$ (**ICU patients**) receiving continuous infusion **(a, c)** and intermittent dosing regimen **(b, d)** on the basis of our proposed dosing guideline (see **Figures 4.4, 4.5**). Dashed lines in the plots of $AUC_{24}$ **(a, b)** represent the targeted efficacy and safety range, while the plots of concentration **(c, d)** represent the defined concentrations corresponding to therapeutic range of the $AUC_{24}$ according to the literature (20~25 mg/L for continuous infusion and 15~20 mg/L for intermittent dosing regimens). The shaded areas represent the 95% prediction interval of the predicted $AUC_{24}$ or concentration. CKD-EPI renal function calculated by the chronic kidney disease epidemiology collaboration equation in (mL/min/1.73 $m^2$), TBW total bodyweight in kg

## 4.4 Discussion

In this study, we quantified vancomycin PK in a large and representative clinical population, covering patients with varying degrees of overweight or obesity and renal function who were admitted to the hospital ward or ICU. Using the obtained insights, we proposed dosing guidelines for both continuous infusion and intermittent dosing regimens taking renal function, bodyweight, and ICU admission status into account. The proposed model-derived regimen is expected to yield better initial dosing and may reduce requirements for dose adjustment. Following our developed dosing guideline, daily $AUC_{24}$/MIC exposure is maintained between 400 and 600 mg h/L in patients with varying degrees of obesity and renal function who are admitted to the hospital ward or ICU. The $AUC_{24}$/MIC target of 400~600 mg·h/L was chosen to ensure clinical efficacy while enhancing patient safety, which is in line with the advice given by the recently released vancomycin consensus guideline [4, 18]. The vancomycin MIC is assumed to be 1 mg/L because the vancomycin MIC for serious infections (e.g., MRSA) is 1 mg/L at most institutions [19]. In cases of increased MIC values, the proposed doses should be increased proportionally, even though, in case the MIC is above 2 mg/L, an alternative agent would probably be preferable.

Achieving targeted $AUC_{24}$ exposures within the initial 24~48 h of the vancomycin treatment course is recommended for early and appropriate therapy [19]. To achieve this, loading doses are necessary. Traditional vancomycin loading doses are administered in mg per kg as a 2-h infusion before the maintenance dose begins. However, on the basis of our model, we developed a dosing guideline for overweight and obese individuals with varying renal functions that involve two loading doses. For continuous infusion, a loading dose of 1500 mg is given as a 2-h infusion before starting the maintenance infusion on day 1, and another loading dose of 750 mg is given as a 2-h infusion on day 2, after which the maintenance infusion is continued. For intermittent dosing regimen, two loading doses are administered every 12 h on the first day to quickly achieve an effective and safe exposure. Even though this is a deviation from current clinical practice, these loading doses are necessary to achieve effective exposure early in the treatment.

Even though the $AUC_{24}$ reaches the target range for most individuals with the proposed regimen, concentrations tend to fall below the commonly expected target ranges

with continuous infusion and intermittent dosing. This suggests that dose adjustment based on concentration at the early stages of treatment may result in concentration and $AUC_{24}$ values outside the target window at later time points. Therefore, we recommended using $AUC_{24}$ values, rather than solely relying on trough concentration values, to interpret TDM samples to guide dosing adjustments. $AUC_{24}$ values can be accurately and reliably obtained by a Bayesian dose-optimization software program that embeds an appropriate reference population PK model. For overweight and obese patients, especially those with renal dysfunction admitted to ICU, particular attention should be paid as the time to steady-state might be prolonged to over a week, but with the appropriate software and models this will be taken into account properly [20].



Readily available and convenient biomarkers for renal function remain limited in overweight and obese patients, as most of the equations calculating renal function estimates are not confirmed in this population [21]. In fact, the equation of CG, which is commonly used, has been reported to have a low accuracy and high bias in estimating glomerular filtration rate in patients with obesity and should therefore be avoided [22, 23]. In our study, among the renal function estimates available in clinical practice, we found indexed CKD-EPI to be superior to CG and other renal function estimates, in correlation with vancomycin *CL*, which is in line with the vancomycin PK study of Kim *et al.* [24]. Moreover, our study confirmed that in overweight and obese populations, TBW is better correlated with *CL* than other bodyweight descriptors [8]. However, this is not always the case, as for cefazolin and ciprofloxacin, *CL* remains unchanged with different degrees of obesity [25, 26].

In addition to renal function and bodyweight, ICU admission status was identified as a significant independent covariate on *CL*, indicating differences between subjects from ICU and non-ICU. The age of ICU and non-ICU patients is comparable (median [range] values for ICU *versus* non-ICU: 70 [33 – 88] *versus* 71 [35 – 92] years). In addition, the eGFR range is similar between patients in the two settings (ICU 75 [20 – 155] *versus* non-ICU 74 [6 – 137] mL/min/1.73 $m^2$). The potential reason for different *CL* in these two settings could be that rapidly varying disease states of ICU patients can lead to reduced kidney function and limited drug elimination [27], with serum creatinine being an inappropriate and/or late marker to indicate this [28]. Interestingly, Smit *et al.* also identified ICU status as an independent predictor for *CL* in a

comparable gentamicin PK study, reporting a 24.9% reduced *CL* in ICU patients [29]. These results contradict a seeming consensus from several studies indicating an augmented renal clearance (eGFR > 130 mL/min/1.73 $m^2$) in critically ill patients [30–32]. This difference could be because compared with the other studies, our study included patients with more severe concomitant disease, but without trauma or burns. Future research investigating the underlying cause of the decreased *CL* in obese individuals with critical illnesses should be considered.

In this study, we included patients undergoing bariatric surgery receiving a single dose of vancomycin and patients treated with vancomycin for infections, resulting in a group covering a broad spectrum of bodyweight. However, patients with a bodyweight higher than 143 kg all had a good renal function. As a result, our dosing guidelines in this group are based on less evidence compared with the group below 143 kg. Moreover, as our dataset included only 15 patients (6.52%) with extremely poor renal function (CKD-EPI < 30 mL/min/1.73 $m^2$), caution is warranted when employing the proposed dosing recommendation for this subgroup. In addition, the lack of covariates and the large inter-individual variability in volume may be due to the fact that we did not have enough peak samples to fully characterize volume and its covariates. However, for the AUC-targeted dose, *CL* is the primary parameter of interest, whereas volume is mainly related to the time to reach steady state. Because we had many (trough) samples both early after initiation of treatment and after several weeks of treatment, we are convinced that our model can be used for AUC-targeted dosing, which was the overall goal of our study, even though it may not accurately predict the peak concentration reached immediately after a 2-h infusion dose.



## 4.5 Conclusion

When dosing vancomycin in overweight and obese patients, renal function, bodyweight, and ICU admission status should be taken into account to get safe and effective vancomycin exposure. We propose a practical vancomycin dosing guideline for both continuous infusion and intermittent dosing regimens that can be used for this purpose.

# References


1. Seidell JC, Halberstadt J. The global burden of obesity and the challenges of prevention. Ann Nutr Metab. 2015;66(Suppl 2):7–12. https://doi.org/10.1159/000375143.

2. World Health Organization. Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 9 May 2023.

3. Rybak MJ, Lomaestro BM, Rotscahfer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis. 2009;49(3):325–7. https://doi.org/10.1086/600877.

4. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020;77(11):835–64. https://doi.org/10.1093/ajhp/zxaa036.

5. Sault AD, Parent M, Simard C. Methods of therapeutic drug monitoring to guide vancomycin dosing regimens: trough concentration *versus* ratio of area under the curve to minimum inhibitory concentration. Can J Hosp Pharm. 2022;75(2):89–96. https://doi.org/10.4212/cjhp.v75i2.3114.

6. Finch NA, Zasowski EJ, Murray KP, et al. A quasi-experiment to study the impact of vancomycin area under the concentrationtime curve-guided dosing on vancomycin-associated nephrotoxicity. Antimicrob Agents Chemother. 2017;61(12):e01293-e1317. https://doi.org/10.1128/aac.01293-17.

7. Smit C, Wasmann RE, Goulooze SC, et al. Population pharmacokinetics of vancomycin in obesity: finding the optimal dose for (morbidly) obese individuals. Br J Clin Pharmacol. 2020;86(2):303–17. https://doi.org/10.1111/bcp.14144.

8. Zhang T, Smit C, Sherwin CMT, Knibbe CAJ, Krekels EHJ. Vancomycin clearance in obese adults is not predictive of clearance in obese adolescents. Clin Pharmacokinet. 2023;62(5):749 – 59. https://doi.org/10.1007/s40262-023-01227-5.

9. Blouin RA, Bauer LA, Miller DD, Record KE, Griffen WO. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents Chemother. 1982;21(4):575–80. https://doi.org/10.1128/aac.21.4.575.

10. Smit C, Goulooze SC, Brüggemann RJM, Sherwin CM, Knibbe CAJ. Dosing recommendations for vancomycin in children and adolescents with varying levels of obesity and renal dysfunction: a population pharmacokinetic study in 1892 children aged 1 – 18 years. AAPS J. 2021;23(3):53. https://doi.org/10.1208/s12248-021-00577-x.

11. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Progr Biomed. 2005;79(3):241–57. https://doi.org/10.1016/j.cmpb.2005.04.005.

12. Keizer RJ, Karlsson MO, Hooker A. Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. CPT Pharmacomet Syst Pharmacol. 2013;2(6): e50. https://doi.org/10.1038/psp.2013.24.

13. Jonsson EN, Hooker A. Xpose 4 Bestiary. http://xpose.sourceforge.net/bestiarium_v1.0.pdf. Ac-

cessed 12 May 2023.

14. Comets E, Brendel K, Mentré F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. Comput Methods Progr Biomed. 2008;90:154–66. https://doi.org/10.1016/j.cmpb.2007.12.002.

15. Zasowski EJ, Murray KP, Trinh TD, et al. Identification of vancomycin exposure-toxicity thresholds in hospitalized patients receiving intravenous vancomycin. Antimicrob Agents Chemother. 2018;62(1):e01684-e1717. https://doi.org/10.1128/aac.01684-17.

16. Heil EL, Claeys KC, Mynatt RP, et al. Making the change to area under the curve-based vancomycin dosing. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm. 2018;75(24):1986–95. https://doi.org/10.2146/ajhp180034.

17. Meng L, Wong T, Huang S, et al. Conversion from vancomycin trough concentration-guided dosing to area under the curveguided dosing using two sample measurements in adults: implementation at an academic medical center. Pharmacotherapy. 2019;39(4):433–42. https://doi.org/10.1002/phar.2234.

18. He N, Su S, Ye Z, et al. Evidence-based guideline for therapeutic drug monitoring of vancomycin: 2020 update by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. Clin Infect Dis Off Publ Infect Dis Soc Am. 2020;71(Suppl 4):S363–71. https://doi.org/10.1093/cid/ciaa1536.

19. Rybak MJ, Le J, Lodise TP, et al. Executive summary: therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Pharmacother J Hum Pharmacol Drug Ther. 2020;40(4):363–7. https://doi.org/10.1002/phar.2376.

20. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin Pharmacokinet. 1986;11(4):257–82. https://doi.org/10.2165/00003088-198611040-00001.

21. Zhang T, Krekels EHJ, Smit C, Knibbe CAJ. Drug pharmacokinetics in the obese population: challenging common assumptions on predictors of obesity-related parameter changes. Expert Opin Drug Metab Toxicol. 2022;18(10):657–74. https://doi.org/10.1080/17425255.2022.2132931.

22. Donker EM, Bet P, Nurmohamed A, et al. Estimation of glomerular filtration rate for drug dosing in patients with very high or low body mass index. Clin Transl Sci. 2022;15(9):2206 – 17. https://doi.org/10.1111/cts.13354.

23. Delanaye P, Björk J, Courbebaisse M, et al. Performance of creatininebased equations to estimate glomerular filtration rate with a methodology adapted to the context of drug dosage adjustment. Br J Clin Pharmacol. 2022;88(5):2118–27. https://doi.org/10.1111/bcp.15132.

24. Kim DJ, Lee DH, Ahn S, et al. A new population pharmacokinetic model for vancomycin in patients with variable renal function: therapeutic drug monitoring based on extended covariate model using CKD-EPI estimation. J Clin Pharm Ther. 2019;44(5):750–9. https://doi.org/10.1111/jcpt.12995

25. Brill MJE, Houwink API, Schmidt S, et al. Reduced subcutaneous tissue distribution of cefazolin in morbidly obese *versus* non-obese patients determined using clinical microdialysis. J Antimicrob Chemother. 2014;69(3):715–23. https://doi.org/10.1093/jac/dkt444.

26. van Rhee KP, Smit C, Wasmann RE, et al. Ciprofloxacin pharmacokinetics after oral and intravenous administration in (morbidly) obese and non-obese individuals: a prospective clinical study. Clin Pharmacokinet. 2022;61(8):1167–75. https://doi.org/10.1007/s40262-022-01130-5

27. Laguado SA, Vadiei N, Yenina K. Impact of recent methamphetamine use on vancomycin clearance. Psychopharmacol Bull. 2020;50(3):23–35.

28. Teo SH, Endre ZH. Biomarkers in acute kidney injury (AKI). Best Pract Res Clin Anaesthesiol. 2017;31(3):331–44. https://doi.org/10.1016/j.bpa.2017.10.003.

29. Smit C, van Schip AM, van Dongen EPA, Brüggemann RJM, Becker ML, Knibbe CAJ. Dose recommendations for gentamicin in the real-world obese population with varying body weight and renal (dys)function. J Antimicrob Chemother. 2020;75(11):3286–92. https://doi.org/10.1093/jac/dkaa312.

30. Cook AM, Hatton-Kolpek J. Augmented renal clearance. Pharmacotherapy. 2019;39(3):346 – 54. https://doi.org/10.1002/phar.2231.

31. Chen IH, Nicolau DP. Augmented renal clearance and how to augment antibiotic dosing. Antibiot Basel Switz. 2020;9(7):393. https://doi.org/10.3390/antibiotics9070393.

32. Chu Y, Luo Y, Jiang M, Zhou B. Application of vancomycin in patients with augmented renal clearance. Eur J Hosp Pharm Sci Pract. 2020;27(5):276 – 9. https://doi.org/10.1136/ejhpharm-2018-001781.

# Supplementary Material

**Table S4.1** Equations used for different bodyweight descriptors and renal function estimates.

| Covariate | Equation | Reference |
|---|---|---|
| **Body weight descriptors** | | |
| TBW (kg ) | – | - |
| BMI (kg/m$^2$) | $TBW/Height^2$ | - |
| BSA (m$^2$) | $\sqrt{TBW \times Height/3600}$ | [1] |
| IBW (kg) | Male: $50.0 + 2.3 \times (Height \times 0.3937 - 60)$<br>Female: $45.5 + 2.3 \times (Height \times 0.3937 - 60)$ | [2] |
| ABW (kg) | $IBW + 0.4 \times (TBW - IBW)$ | [3] |
| LBW (kg) | Male: $(9.27 \times 10^3 \times TBW)/(6.68 \times 10^3 + 216 \times BMI)$<br>Female: $(9.27 \times 10^3 \times TBW)/(8.78 \times 10^3 + 244 \times BMI)$ | [4] |
| **Renal function estimates** | | |
| Indexed CKD-EPI (mL/min/1.73m$^2$) | Male & Scr ≤ 0.9 (mg/dL): $141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age} \times F$<br>Male & Scr > 0.9 (mg/dL): $141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age} \times F$<br>Female & Scr ≤ 0.7 (mg/dL): $141 \times (Scr/0.7)^{-0.329} \times 0.993^{Age} \times F$<br>Female & Scr > 0.7 (mg/dL): $141 \times (Scr/0.7)^{-1.209} \times 0.993^{Age} \times F$<br>F: if black people, F = 1.15, otherwise F = 1 | [5] |
| De-indexed CKD-EPI (mL/min) | $CKD\text{-}EPI \times BSA/1.73$ | |
| Indexed MDRD (mL/min/1.73m$^2$) | Male: $175 \times (Scr/88.4)^{-1.154} \times Age^{-0.203} \times F$<br>Female: $175 \times (Scr/88.4)^{-1.154} \times Age^{-0.203} \times 0.742 \times F$<br>F: if black people, F = 1.212, otherwise F = 1 | [6] |
| De-indexed MDRD (mL/min) | $MDRD \times BSA/1.73$ | |
| CG-TBW (mL/min) | Male: $(140 - Age) \times TBW/(0.815 \times Scr)$<br>Female: $(140 - Age) \times TBW/(0.815 \times Scr) \times 0.85$ | [7] |
| CG-LBW (mL/min) | Male: $(140 - Age) \times LBW/(0.815 \times Scr)$<br>Female: $(140 - Age) \times LBW/(0.815 \times Scr) \times 0.85$ | [8] |

TBW, total bodyweight; LBW, lean bodyweight; ABW, adjusted bodyweight; BSA, body surface area; BMI, body mass index; CKD-EPI, renal function calculated by chronic kidney disease epidemiology collaboration; MDRD, renal function calculated by modification of diet in renal disease; CG-TBW, renal function calculated by Cockcroft-Gault with total bodyweight (conventional); CG-LBW, renal function calculated by CG calculated with lean bodyweight; Scr, serum creatinine.

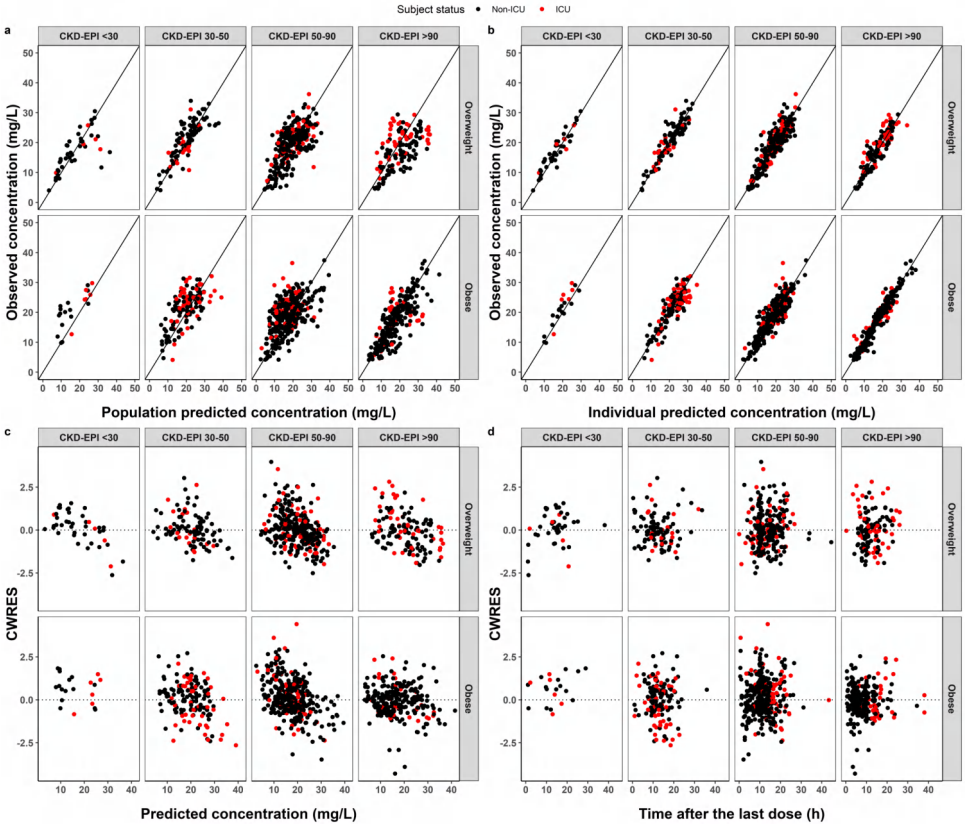



**Figure S4.1** Goodness-of-fit plots of the final pharmacokinetic model for vancomycin in overweight and obese adults. **(a)** observed concentration *versus* population predicted concentration; **(b)** observed concentration *versus* individual predicted concentration; **(c)** conditional weighted residuals (CWRES) *versus* population predicted concentration; **(d)** CWRES *versus* time after the last dose. Black dots represent non-ICU patients, red dots represent ICU patients. Indexed CKD-EPI represents the estimated renal function calculated by chronic kidney disease epidemiology collaboration in mL/min/1.73m$^2$.

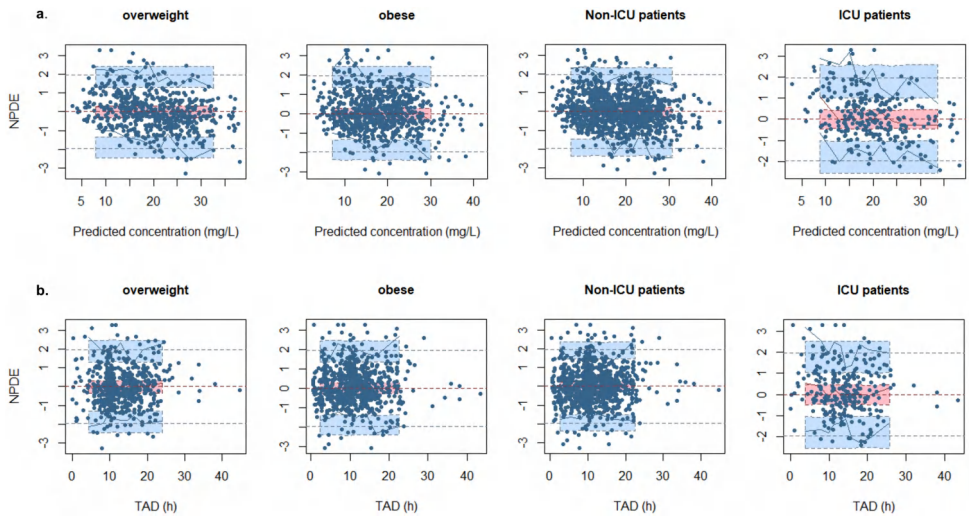



**Figure S4.2** Normalized prediction distribution error (NPDE) *versus* **(a)** population predicted concentrations and **(b)** time after last dose (TAD) of the final model for vancomycin, based on 1000 simulations. Plots are stratified on bodyweight (overweight *versus* obese) and ICU-admission status (non-ICU *versus* ICU). The blue dots represent the NPDE of the observations. The dashed lines represent the theoretical 5$^{th}$, 50$^{th}$, and 95$^{th}$ percentiles of the NPDE. The color shaded areas represent the 95% confidence intervals around the simulated 5$^{th}$, 50$^{th}$, and 95$^{th}$ percentiles. The solid lines represent the 5$^{th}$, 50$^{th}$, and 95$^{th}$ percentiles of the observed NPDE values.

# Supplementary References


1. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317(17):1098.
2. McCarron M, Devine B. Gentamicin therapy. Drug Intell Clin Pharm 1974;8:650–5
3. Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. Eur J Clin Pharmacol 1983;24(5):643–7.
4. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet 2005;44(10):1051–65.
5. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–12.
6. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247–54.
7. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31–41.
8. Pai MP, Nafziger AN, Bertino JS. Simplified estimation of aminoglycoside pharmacokinetics in underweight and obese adult patients. Antimicrob Agents Chemother 2011;55(9):4006–11.