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Impact of a vancomycin loading dose on the achievement of target vancomycin exposure in the first 24 h and on the accompanying risk of nephrotoxicity in critically ill patients

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Background: The advocated pharmacokinetic/pharmacodynamic (PK/PD) target for vancomycin, AUC/MIC $\geq$ 400 mg·h/L, may not be reached with a conventional fixed starting dose of 1000 mg in critically ill patients, but increasing the dose may cause nephrotoxicity.

Objectives: To evaluate the effect of a weight-based loading dose of 25 mg/kg vancomycin on PK/PD target attainment in the first 24 h (AUC_{0-24}) in critically ill patients and to evaluate whether this increases the risk of acute kidney injury (AKI).

Patients and methods: A prospective observational before/after study was performed in ICU patients, comparing the percentage of vancomycin courses with $AUC_{0-24} \geq 400$ mg·h/L and the incidence of AKI, defined as worsening of the risk, injury, failure, loss of kidney function and end-stage kidney disease (RIFLE) score. The conventional dose group received 1000 mg of vancomycin as initial dose; the loading dose group received a weight-based loading dose of 25 mg/kg. A population PK model developed using non-linear mixed-effects modelling was used to estimate AUC_{0-24} in all patients.

Results: One hundred and four courses from 82 patients were included. With a loading dose, the percentage of courses achieving $AUC_{0-24} \geq 400$ mg·h/L increased significantly from 53.8% to 88.0% ($P = 0.0006$). The percentage of patients with new-onset AKI was not significantly higher when receiving a 25 mg/kg loading dose (28.6% versus 37.8%; $P = 0.48$). However, the risk of AKI was significantly higher in patients achieving $AUC_{0-24} > 400$ mg·h/L compared with patients achieving AUC < 400 mg·h/L (39.0% versus 14.8%; $P = 0.031$).

Conclusions: A weight-based loading dose of 25 mg/kg vancomycin led to significantly more patients achieving $AUC_{0-24} \geq 400$ mg·h/L without increased risk of AKI. However, some harm cannot be ruled out since higher exposure was associated with increased risk of AKI.

Introduction

Vancomycin is a glycopeptide antibiotic used in the treatment of infections caused by Gram-positive bacteria, including MRSA, methicillin-resistant CoNS and *Enterococcus faecium*,[1] which occur in particular in the critically ill.

In patients treated with vancomycin for MRSA bloodstream infections, achievement of an adequate AUC/MIC ratio in the first 24 h is associated with a significant decrease in treatment failure and 30 day mortality.[2] Recently revised guidelines on vancomycin dosing are aimed at achieving an AUC/MIC between 400 and 600 mg·h/L for MRSA infections.[3] There is some evidence that the same target could be used for enterococcal infections.[4] Critically ill patients are at risk of undertreatment in the first 24 h, because of an increased volume of distribution and augmented renal

clearance.[5] In the Netherlands, the conventional vancomycin starting dose is 1000 mg,[6] which was also used at the ICU at our hospital, followed by therapeutic drug monitoring (TDM) within the first 48 h. However, guidelines suggest using a vancomycin loading dose of 25–35 mg/kg (based on total body weight) in critically ill patients, since this has been found to decrease the risk of subtherapeutic serum concentrations in the first 24–72 h.[3,7–12] But increasing the dosage can come at a price, since daily AUC values >600–800 mg·h/L are associated with increased risk of vancomycin-associated nephrotoxicity.[13]

The aims of this study were to evaluate the effect of the introduction of a weight-based loading dose of 25 mg/kg on vancomycin AUC target attainment in the first 24 h (AUC_{0-24}) in critically ill patients and to evaluate whether this loading dose significantly increased the risk and/or severity of new-onset nephrotoxicity or contributed to prolonged duration of acute kidney injury (AKI) or mortality during ICU stay.

Patients and methods

Patients and data

A prospective observational before/after study was performed in all adult patients in whom treatment with vancomycin was started at the ICU of Amsterdam UMC, location Academic Medical Center, between December 2013 and April 2014 and between October 2014 and December 2014 and from whom blood samples were available. Patients were eligible for multiple inclusions, but only if at least 72 h existed between the last dose of the first treatment course and the first dose of the second course. The Human Research Ethics Committee of the Amsterdam UMC had taken notice of the study protocol and decided that no ethical approval was required, given that anonymous data from routine diagnostic databases were used.

A new vancomycin loading dose protocol was initiated in January 2014. Included treatment courses were divided into three groups (Figure 1). Courses included in the study before introduction of the loading dose started with a fixed first vancomycin dose of 1000 mg (December 2013 to January 2014). These patients were included in the conventional dose (CD) group. After introduction, patients received a weight-based loading dose of 25 mg/kg with a maximum of 2500 mg (after January 2014). These courses were included in the loading dose (LD) group. However, some patients were accidentally not given a loading dose but a fixed first vancomycin dose despite the introduction of a new protocol (so following the old protocol). These courses were considered to be in the CD group. The third group consisted of courses that accidentally received a loading dose <25 mg/kg or >25 mg/kg.

After the first dose, patients were treated with 1000 mg vancomycin twice a day followed by TDM. A trough serum concentration was measured within 48 h, or before the first maintenance dose in patients with impaired renal function (estimated glomerular filtration rate <60 mL/min).

Blood samples were collected both routinely for TDM and from waste material used for blood gas analyses. The exact time of vancomycin

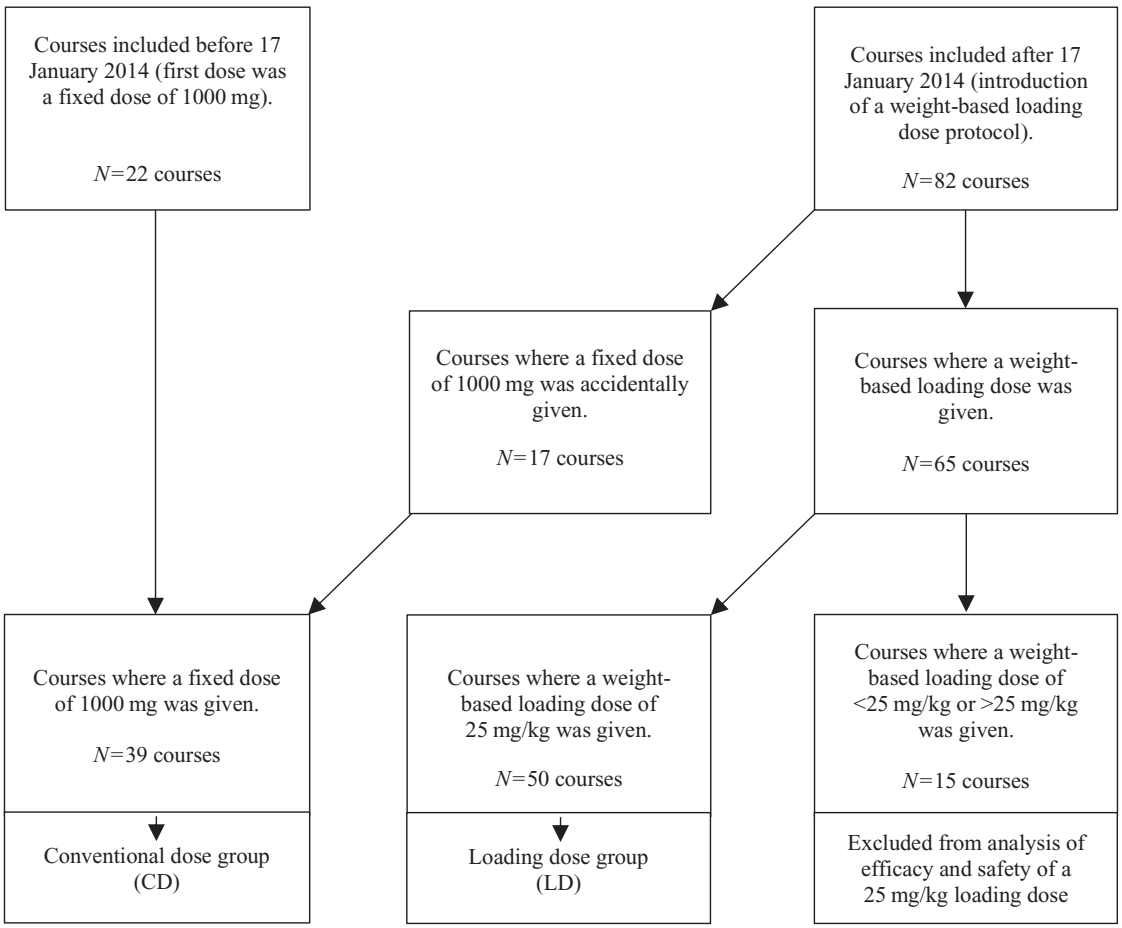

Figure 1. Group allocations.

administration and of sample collection was recorded. Samples were collected from an arterial catheter and stored at room temperature for a maximum of 3 days, until samples were processed.[14] The samples were centrifuged (2750 **g** for 10 min at 20°C) and plasma was frozen at −80°C until samples were analysed. The blood sample collection and processing was standardized in accordance with the quality standards of the Dutch accreditation body CCKL (which transferred to ISO 15189 in 2019). Vancomycin plasma concentrations were measured by automated immunoassay using COBAS INTEGRA 400 plus (Roche Diagnostics, Basel, Switzerland).[15] The limit of quantification was 0.74 mg/L and the assay showed linearity from 3 to 80 mg/L.

The following patient-related parameters were collected from the electronic patient data monitoring system or calculated from these parameters: age, sex, height and total bodyweight (TBW). At the start of therapy, baseline serum creatinine (SCr), the presence of severe neutropenia (defined as an absolute neutrophil count $<0.5 \times 10^9$ cells/L) and severity of disease as assessed by the APACHE II score were noted.[16] During therapy, daily SCr and daily diuresis were noted. CL_{CR} was calculated using the Cockcroft and Gault formula (CRGT).[17] Patients with continuous venovenous haemofiltration (CVVH), were noted on/off for each event. The use of other nephrotoxic medication [aminoglycosides, piperacillin/tazobactam, trimethoprim/sulfamethoxazole, (val)aciclovir, (val)ganciclovir, liposomal amphotericin B, voriconazole, angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors] was noted. Additionally, the source of infection, use of concomitant antibiotics and the pathogens that were isolated, including their antimicrobial susceptibility testing results, were collected.

The outcome of first interest was the percentage of vancomycin courses with AUC ≥ 400 mg·h/L in the first 24 h of therapy (assuming MIC = 1 mg/L). Other endpoints of interest were incidence of new-onset AKI during treatment with vancomycin, duration of AKI during ICU stay, maximum risk, injury, failure, loss of kidney function and end-stage kidney disease (RIFLE) score during ICU stay, use of CVVH at ICU discharge, AKI at ICU discharge and mortality during ICU stay.

Pharmacokinetic (PK) analysis

Vancomycin concentration–time data were analysed using non-linear mixed-effects modelling (NONMEM 7.3; Icon Development Solutions, Ellicott City, MD, USA).[18] Pirana 2.9.4 (Pirana Software & Consulting BV, The Netherlands) was used as the modelling environment.[19]

Firstly, a population PK model of vancomycin in critically ill patients was developed. The first-order conditional estimate method with interaction (FOCE+I) was used. One-, two- and three-compartment PK models were fitted on log-transformed data. Additive, proportional and combined error models were tested to describe the residual variability. Interindividual variability (IIV) and interoccasion variability (IOV) were separately tested for all PK parameters, with each new dose being defined as a new occasion. PK parameters were normalized by allometric scaling.[20]

In the population model, several measures for renal function (CRGT, RIFLE score, RIFLE score based only on SCr), the use of CVVH, age and sex were tested as covariates, explaining interpatient variability. These covariates were added in a stepwise manner to evaluate whether addition led to a statistically significant improvement of the model (forward inclusion). An intermediate covariate model with all statistically significant covariates was constructed, after which a backward elimination procedure was performed. Covariate data were considered missing if they were not available from the day that the sample was drawn for vancomycin concentration measurement. Concentration–time data from patients for whom covariate data were missing were ignored in estimating the correlation between the PK parameter and the covariate, as described earlier.[21]

A decrease in the objective function value (OFV) of ≥3.84, corresponding to $P < 0.05$ in a χ^2 distribution with one degree of freedom, was considered a statistically significant improvement of the model. For the backward elimination procedure, covariates were only retained in the final model if elimination of the covariate led to a rise in OFV of ≥10.8, corresponding to $P < 0.001$. Additionally, the precision of PK parameter estimation and goodness-of-fit plots were evaluated. Goodness-of-fit plots were generated using Xpose 4.5.3 (Uppsala, Sweden)[22] and R 3.4.1.

A bootstrap analysis with replacement (1000 samples) was used for determination of 95% CI of the parameters. Prediction-corrected visual predictive checks (VPCs) were performed to assess the predictive performance of the final model by simulating 1000 patients. VPCs and bootstrap analyses were performed using Perl-speaks-NONMEM 4.6.0.[23]

Assessment of vancomycin AUC_{0-24}

The AUC_{0-24} was estimated in all courses using the empirical Bayes parameter estimates from the final population PK model.

Analysis of other endpoints

New-onset AKI was defined as worsening of the RIFLE score during a course with vancomycin, or achieving a RIFLE score of ≥1 during a course with vancomycin if patients did not meet the criteria for a RIFLE score at the start of vancomycin therapy.[24] A 50% increase of SCr from baseline or urinary output <0.5 mL/kg/h during >6 h were classified as RIFLE score 1, a 100% increase of SCr or urinary output <0.5 mL/kg/h during >12 h were classified as RIFLE score 2 and a 200% increase of SCr or urinary output <0.3 mL/kg/h during >24 h or a SCr ≥350 μmol/L in the setting of an acute rise of SCr ≥44 μmol/L were classified as RIFLE score 3. Patients starting CVVH were also considered to have RIFLE score 3.

Duration of AKI was defined as the number of hours between the first laboratory result showing ≥50% increase of SCr from baseline and the first laboratory result showing return of SCr below 1.5× baseline. If AKI was still present at ICU discharge or death, patients were excluded from analysis of duration of AKI. For patients on CVVH or other renal replacement therapy (RRT), return of SCr below 1.5× baseline was not considered to end the duration of AKI. If patients recovered from AKI but subsequently developed a second episode of AKI (during the same ICU admission or during a second ICU admission), this was considered a separate event.

In addition to the analysis of new-onset AKI during vancomycin treatment (using the maximum RIFLE score during the vancomycin course), the same analysis was performed using the maximum RIFLE score during the complete ICU stay, including both the period during vancomycin treatment and the period after vancomycin treatment had been ended.

Statistical analysis

Descriptive statistics were used to present the data. Data were presented as mean ± SD, unless stated otherwise. Unpaired *t*-test (for normally distributed continuous variables in two groups), Mann–Whitney *U*-test (for non-normally distributed continuous variables in two groups), Fisher's exact test (for binary categorical variables in two groups) and χ^2 test (for nominal categorical variables in two groups) were used to evaluate differences in baseline characteristics of patients without versus with loading dose. Unpaired *t*-test, χ^2 test, Fisher's exact test and one-way ANOVA test (for normally distributed continuous variables in more than two groups) were used to evaluate differences between treatment groups in endpoints. A *P* value of <0.05 was considered to be statistically significant.

Results

A total of 104 vancomycin courses from 82 patients receiving a total of 544 doses of vancomycin (median 4 doses per course, IQR 2–8) were included, yielding 609 vancomycin concentrations (median 4.5 concentrations per course, IQR 2–8), of

Table 1. Baseline characteristics

	All episodes included for model building ($N = 104$)	Episodes without loading dose (CD group) ($N = 39$)	Episodes with 25 mg/kg loading dose (LD group) ($N = 50$)	*P* value
Male (%)	56.7	66.7	50.0	0.13
Age (years)	58.8 ± 14.0	60.1 ± 14.8	59.4 ± 13.0	0.82
Height (cm)	172.3 ± 12.0	172.1 ± 12.6	172.2 ± 12.0	0.96
TBW (kg)	76.2 ± 16.6	73.8 ± 13.4	78.1 ± 19.4	0.60
Obesity (BMI > 30 kg/m^2) (%)	10.6	7.7	14.0	0.50
Starting dose (mg)	1477 ± 538	1000 ± 0	1889 ± 398	<0.0001
Starting dose (mg/kg)	19.8 ± 6.1	14.0 ± 2.8	24.4 ± 1.8	<0.0001
Treatment duration (h)	89.8 ± 58.5	86.6 ± 51.1	92.3 ± 64.5	0.89
Cumulative AUC (mg·h/L)	1937 ± 1448	1849 ± 1359	2027 ± 1543	0.60
APACHE II score	18.7 ± 7.0	19.0 ± 7.3	19.5 ± 6.7	0.70
Severe neutropenia (%)	6.7	2.6	10.0	0.22
SCr at study entry (μmol/L)	138 ± 120	167 ± 163	132 ± 80	0.78
CL_{CR} at study entry (mL/min)	87.6 ± 65.7	80.0 ± 62.4	81.0 ± 60.4	0.81
Median number (range) of nephrotoxic drugs concomitantly administered	0 (0–3)	0 (0–2)	0 (0–3)	0.10
Courses with concomitant administration of nephrotoxic drugs (%)	50.0	43.6	58.0	0.20
Courses with concomitant administration of gentamicin (%)	35.6	35.9	42.0	0.66
CVVH at any time during vancomycin treatment (%)	33.7	35.9	36.0	>0.99

Reported as mean ± SD, unless stated otherwise. Patients with more than one course are included multiple times. *P* value reflects differences between all episodes without versus with 25 mg/kg loading dose. *P* value was calculated using unpaired *t*-test for age, height and APACHE II score, using Fisher's exact test for sex, obesity (yes/no), severe neutropenia (absolute neutrophil count $< 0.5 \times 10^9$ cells/L) (yes/no), percentage of courses with concomitant administration of nephrotoxic drugs (and specifically gentamicin) and CVVH (yes/no), using Mann–Whitney *U*-test for TBW, starting dose (mg), starting dose (mg/kg), SCr at study entry, CL_{CR} at study entry, treatment duration and cumulative AUC and using χ^2 test for the number of concomitant nephrotoxic drugs, including aminoglycosides, piperacillin/tazobactam, trimethoprim/sulfamethoxazole, (val)aciclovir, (val)ganciclovir, liposomal amphotericin B, voriconazole, angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors. Nephrotoxic drugs that were given as co-medication in at least 5% of all courses were also included separately in the table.

which 178 were taken in the first 24 h (median 2 concentrations per course, IQR 1–3).

Baseline characteristics are reported in Table 1 and group allocations are illustrated in Figure 1. The CD group consisted of 39 courses of 35 patients; the LD group, receiving a loading dose of 25 mg/kg with a maximum of 2500 mg, consisted of 50 courses of 45 patients. Two patients had courses in all three treatment groups, 9 patients had courses in two of the three treatment groups and 71 patients had one or more courses in only one of the treatment groups. There were 15 courses of 15 patients where a loading dose of <25 mg/kg ($n = 12$) or >25 mg/kg ($n = 3$) was accidently given. PK data from all three groups were included in the population PK analysis and for the analysis of the association between AUC_{0-24} and the incidence of AKI. Data from the CD and LD groups were used for the analysis of the effect of a loading dose on vancomycin AUC target attainment.

The median vancomycin starting dose was 25.0 mg/kg (IQR 23.2–25.3) in the LD group versus 13.3 mg/kg (IQR 11.8–15.9) in the CD group ($P < 0.0001$). There were no statistically significant differences between groups in baseline characteristics, including renal function at the start of vancomycin therapy (see Table 1).

Only six courses consisted of vancomycin monotherapy. Most patients were treated with a combination of antibiotics (on average 2.8 antibiotics including vancomycin), where vancomycin was added to also empirically treat infections with CoNS, enterococci and sporadically MRSA (in the Netherlands, approximately 99% of *Staphylococcus aureus* isolates are MSSA, so patients suspected of *S. aureus* infection are only treated with vancomycin if they have risk factors for MRSA carriage).

The sources of infection in the 104 courses were predominantly abdominal infection and catheter-related bloodstream infection (43 and 27 courses, respectively, of which 3 cases had both). Other sources were meningitis (17 courses), neutropenic sepsis (5 courses), sepsis of unknown origin (5 courses), severe skin and soft tissue infections (4 courses), post-operative mediastinitis after cardiac surgery (4 courses) and prosthetic vascular graft infection (2 courses).

In 41 of 104 courses, a pathogen was cultured that was treated with vancomycin either empirically or as directed therapy and was not covered with any other antibiotics that the patient received. In 6 of these courses, two pathogens were isolated; the remaining 35 showed one pathogen. There were 22 blood culture isolates:

8 enterococci (4 *E. faecium*, 3 *Enterococcus faecalis*, 1 *Enterococcus gallinarum*) and 14 staphylococci [8 *Staphylococcus epidermidis*, 3 *Staphylococcus hominis*, 2 *S. aureus* (MSSA) and 1 *Staphylococcus capitis*]. Additionally, there were 25 isolates from other, normally sterile body sites that were deemed clinically relevant: 15 enterococci (12 *E. faecium*, 3 *E. faecalis*), 9 staphylococci (7 *S. epidermidis*, 1 *S. aureus*, 1 *Staphylococcus haemolyticus*) and 1 *Rothia mucilaginosa* isolate from CSF samples of a neutropenic patient with meningitis. No cases of MRSA or VRE infection were found.

Model

The data were best described with a two-compartment model with first-order elimination. IIV for CL, *V1* and *V2* and estimation of IOV for *V1* could be estimated. An additional error model best described the residual variability. Allometric scaling of all PK parameters to 70 kg TBW significantly improved the fit of the model to the data (OFV decrease of 95 units). Furthermore, renal function (both RIFLE score and CRGT) was statistically significantly associated with vancomycin clearance, since addition of RIFLE score or CRGT as a covariate for vancomycin clearance led to a significant improvement in fit of the model to the data. CRGT (OFV decrease of 92 units; $P < 0.001$) performed statistically better than the RIFLE score (OFV decrease of 16 units; $P < 0.001$). The addition of age, sex and the use of CVVH as covariates did not improve the model.

Parameter estimates are reported in Table 2 and goodness-of-fit plots in Figure 2. Of the 609 concentration–time data, 15 (2.5%) had missing data for CL_{CR}, but this had no effect on parameter estimates, given that the correction parameter when CRGT is missing was 0.99, so very close to 1. VPC of the final model showed that the model could adequately predict the vancomycin concentrations in the first 24 h, although there was a slight underestimation of vancomycin concentrations at the end of the dosing interval (Figure 3).

The results of the bootstrap of the final model matched the results of the final model well (Table 2).

Analysis of vancomycin AUC_{0-24}

The empirical Bayes estimates resulting from the final population PK model were used to estimate AUC_{0-24} for the individual patients. Use of a loading dose resulted in a higher percentage of courses achieving $AUC_{0-24} \geq 400$ mg·h/L compared with the group receiving standard care (88.0% versus 53.8%; $P = 0.0006$ using Fisher's exact test). Also, use of a loading dose resulted in a median AUC_{0-24} of 602 mg·h/L (range 306–1212), which was higher than in the group receiving standard care [401 mg·h/L (range 200–683); $P < 0.0001$ using Mann–Whitney *U*-test] (see Figure 4).

Analysis of new-onset AKI

Although the percentage of patients with new-onset AKI was numerically higher in the group of patients who received a loading

Table 2. Parameter estimates

	Final model			Bootstrap of final model	
Parameter	Estimate	RSE (%)	Shrinkage (%)	Median	95% CI
CL (L/h)[a]	1.86	6		1.83	1.65–2.08
V1 (L)[b]	13.4	14		13.1	9.6–21.9
Q (L/h)[c]	7.57	7		7.56	5.78–10.03
V2 (L)[d]	36.9	7		35.7	30.5–42.7
IIV					
CL (CV%)[e]	49.2	12	14	50.8	40.0–59.0
V1 (CV%)[e]	128.9	13	23	135.7	75.5–192.0
V2 (CV%)[e]	68.3	11	24	68.2	43.2–86.8
IOV					
V1 (CV%)[e]	58.2	17	64	58.1	42.6–77.2
Residual variability					
Additive error	0.209	2		0.207	0.166–0.256
Covariate effects					
CRGT on CL	0.65	8		0.63	0.46–0.84
Correction parameter when CRGT is missing	0.99	33		0.98	0.62–1.28

RSE, relative standard error; CL, vancomycin clearance; *V1*, vancomycin central volume of distribution; Q, vancomycin intercompartmental clearance; *V2*, vancomycin peripheral volume of distribution.

[a] $CL = 1.86 \times (TBW/70)^{0.75} \times (CRGT/83)^{0.65 \times FLG} \times 0.99^{(1-FLG)} \times e^{\eta IIVCL}$, where FLG = 1 when CRGT data are available and 0 when CRGT data are missing and where ηIIVCL represents the random-effect parameter for IIV in CL.

[b] $V1 = 13.4 \times (TBW/70) \times e^{\eta IIVV1 + \eta IOVV1}$, where ηV1 represents the random-effect parameter for IIV in *V1* and IOV represents the random-effect parameters for IOV in *V1*.

[c] $Q = 7.57 \times (TBW/70)^{0.75}$.

[d] $V2 = 36.9 \times (TBW/70) \times e^{\eta IIVV2}$, where ηIIVV2 represents the random-effect parameter for IIV in *V2*.

[e] CV% calculated as the square root of $(e^{\omega} - 1) \times 100\%$.

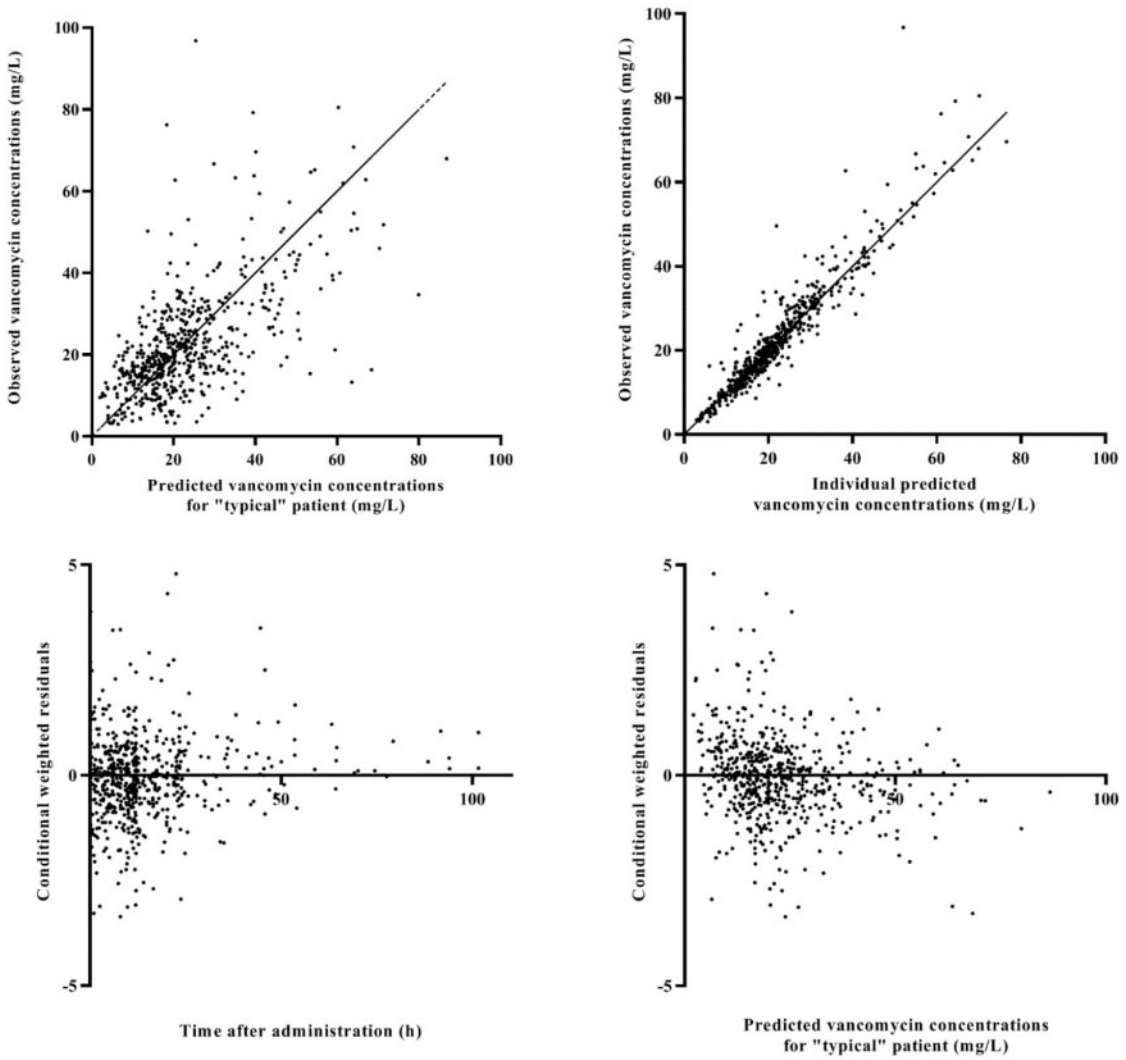

Figure 2. Goodness-of-fit plots of the final population PK model.

dose, this difference was not statistically significant [10/35 (28.6%) in the CD group versus 17/45 (37.8%) in the LD group; $P = 0.48$ using Fisher's exact test]. However, when analysing the association between AUC_{0-24} and new-onset AKI, achieving an $AUC_{0-24} \geq 400$ mg·h/L was associated with a significantly higher incidence of new-onset AKI: 30/77 (39.0%) versus 4/27 (14.8%) compared with patients with an $AUC_{0-24} < 400$ mg·h/L ($P = 0.031$ using Fisher's exact test), resulting in a relative risk of 2.6 (95% CI 1.02–6.78; number needed to harm = 4.1). The same was true for achieving an $AUC_{0-24} \geq 600$ mg·h/L, which is the upper limit of the therapeutic window: 17/35 (48.6%) versus 17/69 (24.6%); $P = 0.017$ using Fisher's exact test.

Analysis of other endpoints

There was no statistically significant difference in mean AKI duration (75.2 h in the CD group versus 37.2 h in the LD group; $P = 0.71$ using Mann–Whitney *U*-test), in percentage of patients with AKI using the maximum RIFLE score during the complete ICU stay (59.4% in the CD group versus 57.5% in the LD group; $P > 0.99$ using Fisher's exact test), in percentage of patients still on CVVH or other RRT at ICU discharge (21.2% in the CD group versus 31.7% in the LD group; $P = 0.43$ using Fisher's exact test), in percentage of patients with AKI at ICU discharge (30.3% in the CD group versus 34.1% in the LD group; $P = 0.81$ using Fisher's exact test) or in mortality during ICU stay (33.3% in the CD group versus 26.8% in the LD group; $P = 0.61$ using Fisher's exact test).

Discussion

We evaluated the effect of a loading dose on vancomycin PK/pharmacodynamic (PK/PD) target attainment in the first 24 h in critically ill patients admitted to the ICU, where AUC_{0-24} for calculation of PK/PD target attainment was estimated using a NONMEM population PK model, which was developed specifically for the purpose of this study. Our results show improved target attainment in the first 24 h of vancomycin treatment when a weight-based loading dose was used, confirming the results of previous studies.[7–12] To the

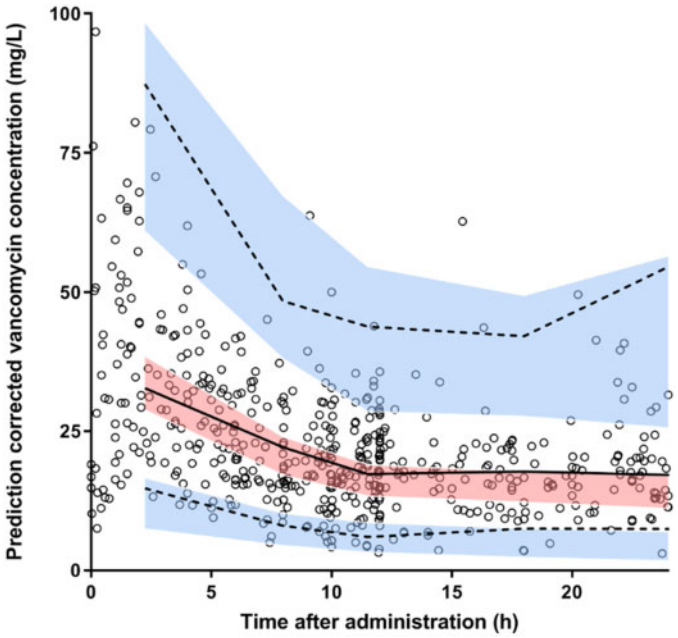

Figure 3. Prediction-corrected VPC of the first 24 h using the final model. The circles represent the observed data. The solid line represents the median and the dotted lines represent 5th and 95th percentiles of the observed data. The shaded regions summarize the predicted 95% CIs of the median/percentile in that bin. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

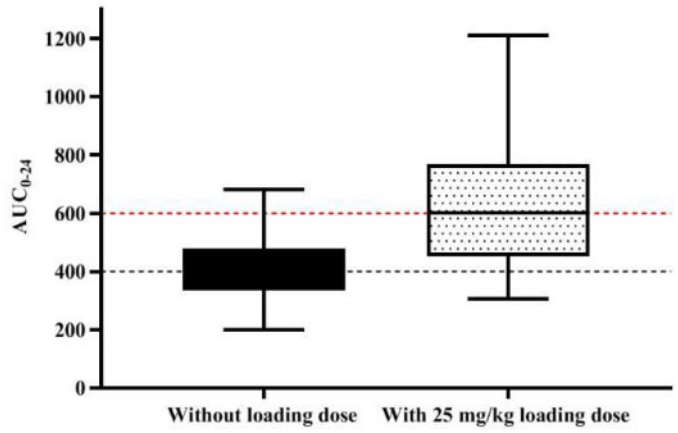

Figure 4. AUC_{0-24} without ($N = 39$) versus with ($N = 50$) 25 mg/kg loading dose. Whiskers represent minimum to maximum AUC_{0-24}. The dotted lines represent the lower and upper boundaries of the therapeutic window. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

best of our knowledge, our study is currently the largest study on the effect of a loading dose on vancomycin AUC target attainment, including approximately twice the number of patients and four times the number of samples than in other studies.[11,12] Most previous studies on the effect of a loading dose used vancomycin trough concentrations as target.[7–10] However, trough concentrations underestimate the AUC_{0-24}[25] and AUC-guided vancomycin dosing has been shown to decrease nephrotoxicity without reducing efficacy.[26,27] Therefore the recently updated IDSA/ASHP guideline does not recommend target trough concentrations, but AUC_{0-24}.[3] Two smaller studies including 41 patients (of which 23 were treated with a loading dose) and 45 patients (of which 8 were treated with a loading dose) showed a significant increase in AUC_{0-24}/MIC target attainment when using a loading dose.[11,12] Both studies used predominantly trough levels and an external population PK model for maximum *a posteriori* Bayesian estimation of AUC_{0-24}. However, they did not report whether this model was valid for their investigated population. We used Bayesian analysis based on a population PK model that was specifically developed for the purpose of this study (leading to more reliable estimation of AUC_{0-24}) and was based on vancomycin concentrations covering the whole dosing interval (Figure 3).[3]

We also evaluated the impact of a vancomycin loading dose on the incidence of nephrotoxicity. No statistically significant difference in incidence of AKI was found between the patient groups with and without a loading dose, nor in mean AKI duration or in other clinically relevant outcomes like mortality during ICU stay. This is in concordance with other studies. A systematic review and meta-analysis of nine studies including 2816 patients found a significantly higher rate of vancomycin trough concentrations of 15–20 mg/L after a loading dose, without an increased risk of nephrotoxicity or other adverse effects.[28] A multicentre, retrospective, cohort study including 316 patients with MRSA bacteraemia found that receipt of vancomycin loading doses >1750 mg was protective against treatment failure, without increasing nephrotoxicity.[29] Of note though, the risk of AKI was significantly higher in patients who achieved an $AUC_{0-24} > 400$ mg·h/L compared with patients who achieved an AUC < 400 mg·h/L and in patients who achieved an $AUC_{0-24} > 600$ mg·h/L compared with patients who achieved an AUC < 600 mg·h/L. These findings do suggest a positive association between vancomycin exposure and risk of new-onset AKI and therefore an increased risk of nephrotoxicity for each increase in AUC. This was also found in earlier observational studies.[30,31] Both studies showed an incidence of nephrotoxicity comparable to the current study (39% in patients with vancomycin AUC > 400 mg·h/L versus 14.8% in patients with AUC < 400 mg·h/L). So while it is clear that higher vancomycin exposure is associated with an increased risk of AKI, it is uncertain whether use of a loading dose poses an additional risk. The additional risk may be limited if the loading dose does not lead to an $AUC_{0-24} > 600$ mg·h/L.[13] However, in our study, 26/50 (52%) of courses with a loading dose led to an $AUC_{0-24} > 600$ mg·h/L (Figure 4). Using TDM to measure the AUC_{0-24} within 48 h after start of vancomycin therapy (within 24 h when renal function is impaired) is therefore essential to identify patients with an $AUC_{0-24} > 600$ mg·h/L and to adjust the maintenance dose accordingly.

Our study shows some limitations. Firstly, CL_{CR} was calculated using CRGT, since more accurate ways were not available. CRGT is known to overestimate the clearance in patients with AKI.[32] Indeed, our model underestimated the vancomycin concentrations at the end of the dosing interval, which is also reflected in the VPC (Figure 3). However, the model described the observed data reasonably well for the first 24 h, which was relevant for calculating AUC_{0-24}. Moreover, CRGT performed statistically better than the RIFLE score, which was also tested as a covariate for vancomycin clearance, leading to a larger decrease in OFV and better goodness-of-fit plots. Since addition of CL_{CR} using CRGT led to a

better model fit and hence to better AUC_{0-24} estimations, it was included in the final model. Secondly, for a profound analysis of the association between vancomycin AUC_{0-24} and new-onset AKI, a multivariate regression analysis would be needed since many comorbidities, co-administered drugs and events during ICU admittance can have a significant impact on the renal function. Unfortunately, our data were insufficiently complete to reliably perform such an analysis. In addition, our main goal was to evaluate the efficacy and safety of a loading dose by comparing the CD group with the LD group. We did not see significantly more AKI after a loading dose, but there are clues using a limited univariate analysis that a higher AUC_{0-24} could form an increased risk of AKI. Thirdly, we used intermittent vancomycin dosing in both treatment groups, but continuous infusion of vancomycin is also increasingly being used as it may be associated with less nephrotoxicity.[33] Our data cannot be extrapolated to continuous infusion, where loading doses are generally lower. Fourthly, this study was carried out at one centre, so the results may not be applicable to other institutions. Fifthly, the sample size of our study was small, also precluding a reliable analysis of the association between AUC_{0-24} and new-onset AKI, and there were no MRSA patients included, which may have limited the ability to identify significant predictors for mortality.

In conclusion, a weight-based loading dose of 25 mg/kg vancomycin led to significantly more patients achieving $AUC_{0-24} \geq 400$ mg·h/L and did not lead to a significantly increased risk of AKI, but some harm cannot be ruled out since higher exposure was associated with increased risk of AKI.

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