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New Regimen for Continuous Infusion of Vancomycin in Critically Ill Patients

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Despite the development of new agents with activity against Gram-positive bacteria, vancomycin remains one of the primary antibiotics for critically ill septic patients. Because sepsis can alter antimicrobial pharmacokinetics, the development of an appropriate dosing strategy to provide adequate concentrations is crucial. The aim of this study was to prospectively validate a new dosing regimen of vancomycin given by continuous infusion (CI) to septic patients. We included all adult septic patients admitted to a mixed intensive care unit (ICU) between January 2012 and May 2013, who were treated with a new vancomycin CI regimen consisting of a loading dose of 35 mg/kg of body weight given as a 4-h infusion, followed by a daily CI dose adapted to creatinine clearance (CrCL), as estimated by the Cockcroft-Gault formula (median dose, 2,112 [1,500 to 2,838] mg). Vancomycin concentrations were measured at the end of the loading dose (T1), at 12 h (T2), at 24 h (T3), and the day after the start of therapy (T4). Vancomycin concentrations of 20 to 30 mg/liter at T2, T3, and T4 were considered adequate. A total of 107 patients (72% male) were included. Median age, weight, and CrCL were 59 (interquartile range [IQR], 48 to 71) years, 75 (IQR, 65 to 85) kg, and 94 (IQR, 56 to 140) ml/min, respectively. Vancomycin concentrations were 44 (IQR, 37 to 49), 25 (IQR, 21 to 32), 22 (IQR, 19 to 28), and 26 (IQR, 22 to 29) mg/liter at T1, T2, T3, and T4, respectively. Concentrations were adequate in 56% (60/107) of patients at T2, in 54% (57/105) at T3, and in 73% (41/56) at T4. This vancomycin regimen permitted rapid attainment of target concentrations in serum for most patients. Concentrations were insufficient in only 16% of patients at 12 h of treatment.

Vancomycin remains a primary treatment for infections caused by Gram-positive bacteria resistant to β-lactam antibiotics, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), and ampicillin-resistant enterococci (1). Despite extensive clinical use of vancomycin over recent years, the optimal dosing strategy for rapid achievement of therapeutic concentrations still remains a challenge for physicians. This is of particular interest for patients with septic shock, who require adequate antibiotic therapy, especially in terms of drug concentrations, from the early phase of treatment (2, 3). To rapidly achieve optimal vancomycin concentrations in such patients, a loading dose followed by a continuous drug infusion (CI) has been proposed (4).

Although CI of vancomycin is increasingly used, especially in the intensive care unit (ICU), there is still a controversy as to whether this mode of administration provides better results than standard intermittent drug administration (II). Several studies have shown no differences in clinical efficacy or mortality between the two therapeutic strategies in infections with Gram-positive bacteria (4–6). However, Wysocki et al. (5) demonstrated that CI allowed faster achievement of target concentrations, presented less variability in drug concentrations, and resulted in reduced costs of therapy. Furthermore, a recent meta-analysis showed that CI was associated with a significantly lower risk of drug-related nephrotoxicity than II, despite the use of similar daily doses (6).

Nevertheless, because of significant changes in vancomycin pharmacokinetics (PK) during critical illness, such as increased volume of distribution (*V*) and augmented clearance, the standard CI regimen (e.g., a loading dose of 15 mg/kg of body weight, followed by 30 mg/kg over 24 h for patients with normal renal function) (5) has been associated with inadequate drug concentrations in a high proportion of septic patients in the first 2 days of therapy (7). As such, Roberts et al. (8), using a population PK analysis, suggested that a vancomycin loading dose of 35 mg/kg, followed by daily doses adjusted to creatinine clearance (CrCL, ranging from 7 to 45 mg/kg/day), would rapidly achieve adequate drug concentrations in critically ill patients. Nevertheless, this approach has not been prospectively validated yet.

Another important issue concerning vancomycin is that clinical efficacy is best predicted when the ratio between the area under the curve of drug concentrations over 24 h (AUC_{0-24}) and the MIC for the pathogen isolated (AUC_{0-24}/MIC) exceeds 400 (9–12). To ensure optimal AUC_{0-24}/MIC ratios, several studies have proposed target serum drug concentrations between 15 and 30 mg/liter during CI of vancomycin (5, 13–15). Nevertheless, no study has evaluated the correlation between vancomycin concentrations and the achievement of an AUC_{0-24}/MIC ratio of ≥400 in critically ill patients, in particular during the first day of therapy.

The aim of this study was, therefore, to determine whether a newly described CI regimen of vancomycin would result in ade-

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TABLE 1 Initial daily doses of vancomycin according to estimated creatinine clearance

CG-CrCL[a] (ml/min)	Daily dose (mg/kg)
>150	45
120–150	40
80–119	30
50–69	25
25–50	14
<25 (anuria)	7

[a] Creatinine clearance, estimated using the Cockcroft-Gault formula.

quate drug concentrations in critically ill patients in the early phase of therapy. We also evaluated whether target vancomycin concentrations could predict optimal AUC_{0-24}/MIC ratios in these patients.

MATERIALS AND METHODS

Patient population. We included all adult (age, ≥18 years) patients who were treated with CI of vancomycin, either as monotherapy or combined with other antibiotics, in our multidisciplinary Department of Intensive Care between January 2012 and May 2013. In January 2012, we introduced a new vancomycin CI regimen as the standard of care for all patients. This regimen consisted of a loading dose of 35 mg/kg given over a 4-h infusion period followed by a CI adapted to the CrCL (8), as assessed using the Cockcroft-Gault equation (CG-CrCL) (16) (Table 1). Total body weight (TBW) was used to calculate the drug regimen; if not available in the medical file, TBW was estimated by the attending physician. This procedure was used because it is routinely used to adjust antibiotic regimens in our Department. Patients were excluded if they had received vancomycin in the preceding 48 h or if they were receiving treatment with any renal replacement therapy or with extracorporeal membrane oxygenation (ECMO). The study protocol was approved by the local Ethics Committee (Comité d'Ethique Hôpital Erasme—ULB), which waived the need for informed consent, because this regimen and drug monitoring are considered routine management in this setting in our department.

Vancomycin therapy. Vancomycin was reconstituted according to the manufacturer's guidelines. Serum drug concentrations were measured in 3-ml blood samples taken at the end of the loading dose (T1), 12 h after the onset of treatment (T2), and 24 h after the onset of treatment (T3). Nurses recorded the exact sampling time on a computer-based database. Serum drug concentrations were also measured daily at 8 am thereafter (i.e., on day 2, day 3, etc.). Vancomycin concentrations were determined by a particle-enhanced turbidimetric inhibition immunoassay (Dimension XPand; Siemens Healthcare Diagnostics, Newark, DE). The limit of quantification and the total imprecision of the assay were 0.8 mg/ml and <5%, respectively. The aim of this regimen was to attain "adequate" serum vancomycin concentrations (i.e., between 20 and 30 mg/liter) at 12 and 24 h. Insufficient or excessive drug concentrations were defined as <20 mg/liter or >30 mg/liter, respectively. In the case of insufficient drug concentrations at T3, a bolus of 500 to 1,000 mg was given, and the daily dose was increased by 25%. If drug levels were excessive, the CI was discontinued for 4 h, and the daily dose was decreased by 25%.

Data collection. For all patients included, the following data were recorded: demographics (including weight and body mass index [BMI]), comorbidities, admission diagnosis, biological and microbiological data, length of ICU and hospital stays, and ICU mortality. The severity of illness was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score (17) on admission for each patient. The Sequential Organ Failure Assessment (SOFA) score (18) was assessed and recorded daily. Patients were said to have chronic kidney disease (CKD) when the estimated glomerular filtration rate was <60 ml/min (i.e., CKD stage 3 to 5, not on dialysis) according to recent definitions (19). Treatment with vasopressor agents or mechanical ventilation was also recorded. We also determined the CrCL at 24 h of therapy based on urinary creatinine excretion (uCrCL [measured in milliliters per minute]), which was routinely calculated every day as (urinary creatinine concentration [in milligrams per deciliter] × volume [in milliliters])/(serum creatinine concentration [in milligrams per deciliter] × duration of urine collection [in minutes]). Augmented renal clearance was defined as a uCrCl of >130 ml/min (20).

Pharmacokinetic parameters. The AUC of serum vancomycin concentrations measured during the first 24 h of treatment was calculated for each patient using the trapezoidal rule. Vancomycin clearance (CL_{VAN}) was calculated as (dose rate)/(concentration at 24 h).

Statistical analysis. Statistical analyses were performed using the SPSS 18.0 for Windows NT software package (2004; SPSS Inc., Chicago, IL, USA). Descriptive statistics were computed for all study variables. A Kolmogorov-Smirnov test was used, and histograms and normal quantile plots were examined to verify the normal distribution of continuous variables. Discrete variables were expressed as counts (percentages) and continuous variables as means ± standard deviations (SD) or medians (ranges). Multivariable logistic regression was used to assess which factors were independently associated with insufficient or excessive vancomycin concentrations at T3; only variables with P values of <0.1 in the univariate analysis were included in the final model. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of vancomycin concentrations of ≥20 mg/liter for predicting an AUC_{0-24}/MIC ratio of ≥400 were calculated for several MICs. Drug concentrations associated with the best sensitivity, specificity, PPV, and NPV were identified. Finally, we divided patients according to the CrCL ranges obtained using the CG-CrCL or the uCrCL into the following groups: (i) group 1, for which both CrCL values were within the same range, corresponding to a particular recommended daily dose (Table 1); (ii) group 2, for which the uCrCL was higher than the CG-CrCL (i.e., patients at risk of underdosing), and (iii) group 3, for which the CG-CrCL was higher than the uCrCL (i.e., patients at-risk of overdosing). Vancomycin concentrations were compared among these groups using two-way analysis of variance (ANOVA), followed by a Bonferroni *post hoc* analysis to evaluate differences between groups for each time point. A P value of <0.05 was considered significant.

RESULTS

A total of 107 patients were included during the study period. Demographic characteristics are shown in Table 2. Most patients were admitted for medical reasons, with a median APACHE II score of 19 on admission and a median SOFA score of 6 at the beginning of the CI. The most frequent sites of infections were the lungs and the abdomen (Table 3). Twenty-four of the proven infections with Gram-positive bacteria were due to MRSA, MRSE, or *Enterococcus faecium* (there were 60 infections with Gram-negative bacteria and 23 negative microbiological samples). All patients were receiving at least one other antimicrobial agent at the moment when the CI of vancomycin was initiated. Twenty-two patients (21%) had augmented renal clearance, and 17 (16%) had a BMI of >30.

The median loading dose of vancomycin was 2,650 mg, and the median daily dose was 2,112 mg. At T1, T2, and T3, median serum vancomycin concentrations were 44, 25, and 22 mg/liter, respectively (Table 4). The distributions of vancomycin concentrations at T1, T2, and T3 are shown in Fig. 1; 17 (16%) and 29 (28%) patients had drug concentrations of <20 mg/liter at T2 and T3, respectively. Concentrations were adequate in 56% (60/107) of patients at T2 and in 54% (57/105) of patients at T3. Levels were excessive in 28% (30/107) and 17% (19/105) of patients at T2 and T3, respectively. Consideration of the distribution of drug con-

TABLE 2 Characteristics of patients

Characteristic[a]	Value for patients[b] ($n = 107$)
Age (yr)	59 (48–71)
No. of men/women	77/30
Body wt (kg)	75 (65–85)
Body mass index (kg/m^2)	24 (22–28)
No. (%) with comorbidities	
COPD/asthma	19 (18)
Heart disease	24 (22)
Diabetes	23 (21)
Chronic renal disease	31 (29)
Liver cirrhosis	7 (6)
Cancer	17 (16)
Corticosteroids	34 (32)
Other immunosuppressive agents	25 (23)
Organ transplantation	17 (16)
No. (%) with medical admission	69 (64)
APACHE II score on ICU admission	19 (13–25)
SOFA score at the onset of therapy	6 (4–9)
No. (%) with septic shock at the onset of therapy	57 (53)
No. (%) on mechanical ventilation at the onset of therapy	58 (54)
ICU mortality (no. [%])	24 (22)

[a] COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit.
[b] Data are presented as counts (percentages) or medians (25th to 75th percentiles).

centrations within the different uCrCL ranges at T3 shows that the patients with the highest uCrCL values had a greater proportion of insufficient drug concentrations than the other patients (Fig. 2) ($P = 0.02$).

The only factors identified as predictors for insufficient serum concentrations at T3 were lower BMI and higher uCrCL (Table 5). Excessive drug concentrations at T3 were predicted by higher BMI, lower uCrCL and higher vancomycin concentrations at T1. Table 6 shows the sensitivity, specificity, PPV, and NPV of vancomycin concentrations for predicting AUC_{0-24}/MIC ratios of ≥400 for several MICs. For a MIC of 1.0 mg/liter, target serum vancomycin concentrations of >15 mg/liter at T3 ensured AUC_{0-24}/MIC ratios of ≥400 mg/h/liter in all the patients. However, for MICs of >1.5 mg/liter, target serum drug concentrations of ≥25 mg/liter were necessary to ensure that most patients (97%) attained adequate PK targets.

TABLE 3 Characteristics of infections

Infection[a]	No. (%) of patients ($n = 107$)
Lung	47 (44)
Abdominal	12 (11)
Urinary	8 (7)
Skin or soft tissue	8 (7)
Catheter related	7 (6)
Neurological	5 (5)
Primary bacteremia	18 (17)
MRSA	10
MRSE	10
Enterococcus faecium	4

[a] MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

TABLE 4 Pharmacokinetic and pharmacodynamic characteristics of therapy

Characteristic[a]	Value for patients[b]
Vancomycin concn (mg/liter)	
At 4 h (T1)	44 (37–49)
At 12 h (T2)	25 (21–32)
At 24 h (T3)	22 (19–28)[c]
On day 2	26 (22–30)[d]
AUC_{0-24} (mg · h/liter)	771 (644–905)
Drug clearance from 0 to 24 h (mg · h/liter)	3.0 (2.1–3.8)
CG-CrCL (ml/min)	94 (56–140)
uCrCl (ml/min)	82 (43–157)

[a] CG-CrCL, creatinine clearance according to the Cockcroft-Gault formula; uCrCL, creatinine clearance determined from urinary elimination.
[b] Data are presented as medians (25th to 75th percentiles). A total of 107 patients were evaluated except where otherwise indicated.
[c] A total of 105 patients were evaluated.
[d] A total of 56 patients were evaluated.

When uCrCL and CG-CrCL values were compared, 47 patients were classified in group 1, 13 in group 2, and 47 in group 3 (thus, 60/107 patients would not receive the adequate daily dose if the CG-CrCL was used). There were significant differences in serum drug concentrations among the three groups, in particular at T2, when concentrations in group 2 were lower than those in the other two groups (Fig. 3). Among those patients for whom the CI was continued after the first day of therapy ($n = 56$), 14 (25%) had insufficient and 12 (21%) had excessive drug concentrations. After adjustment of the drug regimen, only 4 (7%) and 6 (11%) patients had insufficient and excessive drug concentrations on day 2 of therapy, respectively (P, 0.04 versus T3).

DISCUSSION

In this study, we evaluated a new regimen for CI of vancomycin for critically ill patients during the first 24 h of therapy, which in-

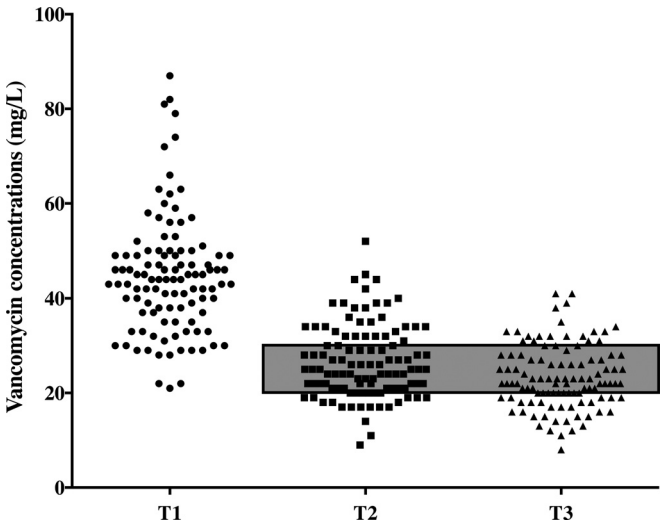

FIG 1 Distribution of vancomycin concentrations at the end of the loading dose (T1), at 12 h (T2), and at 24 h after the onset of therapy (T3). The shaded zone indicates target drug concentrations, assessed at T2 and T3.

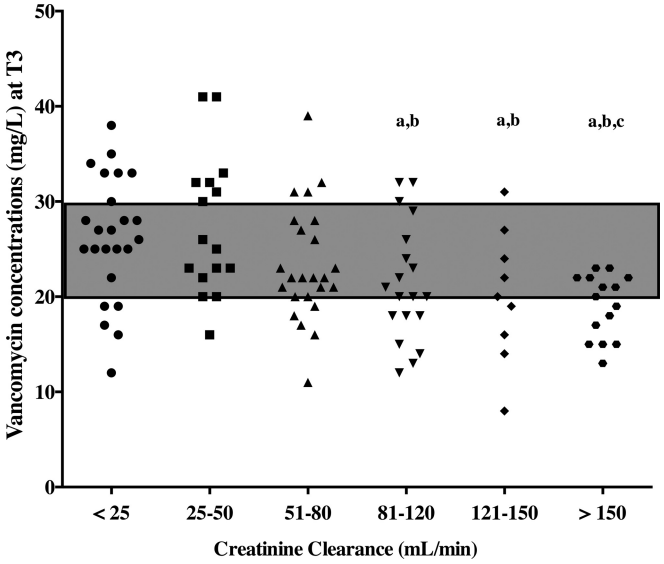

FIG 2 Distribution of vancomycin concentrations at 24 h after the onset of therapy (T3), according to different creatinine clearance values measured from daily urine collection. The shaded zone indicates target drug concentrations. Chi-square analysis for trend yielded a *P* value of 0.02. Lowercase letters a, b, and c above data indicate significant differences. Individual analyses showed significant differences ($P < 0.05$) from vancomycin concentrations at a creatinine clearance of <25 ml/min (a), 25 to 50 ml/min (b), or 51 to 80 ml/min (c).

cluded a higher than recommended loading dose and a daily dose adjusted for renal function. We found that only 16% of patients had insufficient drug concentrations at 12 h, and 28% at 24 h, after the initiation of treatment. After a dosing regimen adjustment at 24 h, >90% of the patients in this cohort eventually achieved minimal target serum drug concentrations within 48 h from the onset of drug infusion. Importantly, one-quarter of the patients had excessive serum drug concentrations during the first day of therapy. The major determinants for insufficient serum concentrations were increased BMI and augmented renal clearance. We also showed that a serum drug concentration of at least 15 mg/liter at 24 h would ensure an adequate AUC_{0-24}/MIC ratio in all patients for strains with a MIC of ≤1.0 mg/liter. However, for infections due to bacteria with MICs of ≥1.5 mg/liter, serum drug concentrations of ≥25 mg/liter would be necessary to achieve adequate AUC_{0-24}/MIC ratios.

For non-ICU patients with severe MRSA infections, standard regimens of vancomycin (15 mg/kg followed by 30 mg/kg/day) given by CI achieved target drug concentrations within 36 h from the initiation of therapy (5). Nevertheless, recent studies have underlined that for critically ill patients, this drug regimen is associated with a high proportion of individuals with insufficient drug concentrations, because of significant changes in vancomycin PK (7, 21). Ocampos-Martinez et al. found that this standard regimen resulted in vancomycin concentrations of <20 mg/liter in >50%

TABLE 5 Risk factors for insufficient or excessive serum vancomycin concentrations at 24 h of treatment (T3)

Characteristic[a]	Value[b] for patients with vancomycin concns (mg/liter) of:		*P* value (<20 vs >20 mg of vancomycin/liter)[b]	Value[c] for patients with vancomycin concns (mg/liter) of:		*P* value (<30 vs >30 mg of vancomycin/liter)[c]
	<20 ($n = 29$)	>20 ($n = 78$)		<30 ($n = 85$)	>30 ($n = 22$)	
Age	56 (37–68)	59 (49–71)	0.07	59 (47–72)	59 (46–70)	0.67
No. (%) male	23 (79)	54 (69)	0.31	63 (74)	14 (64)	0.35
Wt (kg)	56 (65–75)	59 (65–90)	0.007	75 (65–80)	80 (65–95)	0.12
Body mass index (kg/m^2)	24 (22–26)	25 (15–27)	0.01	24 (22–28)	28 (24–30)	0.01
No. (%) with:						
Medical admission	20 (69)	49 (63)	0.56	54 (64)	15 (68)	0.69
Corticosteroids	7 (24)	27 (35)	0.31	28 (33)	6 (27)	0.58
Neutropenia	1 (3)	9 (12)	0.23	8 (9)	2 (9)	0.51
Organ transplant	2 (7)	15 (19)	0.17	15 (18)	2 (9)	0.51
Cancer	4 (14)	13 (17)	0.72	13 (15)	4 (18)	0.99
COPD/asthma	5 (17)	14 (18)	0.93	14 (17)	5 (23)	0.68
Diabetes	7 (24)	16 (21)	0.69	18 (21)	5 (23)	0.58
Heart disease	7 (24)	17 (22)	0.79	19 (22)	5 (23)	0.65
CKD	7 (24)	24 (31)		24 (28)	7 (32)	
Liver cirrhosis	0 (0)	6 (8)	0.99	5 (6)	2 (9)	0.81
APACHE II on admission	20 (15–23)	19 (13–24)	0.97	20 (14–23)	19 (13–23)	0.66
No. (%) in shock	17 (59)	41 (53)	0.63	46 (54)	12 (55)	0.97
No. (%) on mechanical ventilation	18 (62)	40 (51)	0.32	49 (58)	9 (41)	0.25
SOFA score on day 1	6 (3–9)	7 (4–10)	0.91	7 (4–9)	6 (4–10)	0.86
Daily dose of vancomycin (mg/kg)	36.8 (25–42.6)	28.2 (23.5–35.7)	0.19	33.8 (24.0–38.5)	25.8 (25.0–40.0)	0.98
Vancomycin concn (mg/liter) at T1	39 (33–45)	46 (40–50)	0.12	42 (33–47)	50 (46–59)	0.001
No. (%) with respiratory infection	15	32	0.32	39 (46)	8 (36)	0.86
uCrCL (ml/min)	138 (73–178)	64 (33–138)	0.13	97 (51–162)	52 (23–82)	0.02

[a] CKD, chronic kidney disease; T1, end of loading dose infusion; uCrCL, creatinine clearance measured on daily urine excretion.
[b] Obtained by univariate analysis. Multivariate analysis found body mass index (odds ratio [95% confidence interval], 0.87 [0.78 to 0.96]) and uCrCL (1.01 [1.00 to 1.02]) to be predictive of insufficient drug concentrations.
[c] Obtained by univariate analysis. Multivariate analysis found body mass index (odds ratio [95% confidence interval], 1.15 [1.02 to 1.29]), the vancomycin concentration at T1 (1.06 [1.01 to 1.10]), and uCrCL (0.98 [0.97 to 0.99]) to be predictive of excessive drug concentrations.

TABLE 6 Sensitivity, specificity, and positive and negative predictive values of vancomycin concentrations at T3 for predicting AUC_{0-24}/MIC ratios of ≥400 at different MICs[a]

Vancomycin concn (mg/liter) at T3 and predictive measure	Value (%) for predicting an AUC_{0-24}/MIC ratio of ≥400 at a MIC (mg/liter) of:			
	0.5	1.0	1.5	2.0
≥15				
Sensitivity	95	96	100	100
Specificity	100	100	31	6
PPV	100	100	89	26
NPV	0	20	100	100
≥20				
Sensitivity	78	78	87	94
Specificity	100	100	75	37
PPV	100	100	95	57
NPV	0	4	50	88
≥25				
Sensitivity	37	37	43	70
Specificity	100	100	100	93
PPV	100	100	100	90
NPV	0	2	24	78
≥30				
Sensitivity	21	21	24	44
Specificity	100	100	100	100
PPV	100	100	100	100
NPV	0	1	19	67

[a] T3, 24 h after the initiation of therapy; AUC_{0-24}/MIC ratio, ratio between the area under the curve of drug concentrations over the first day of therapy and the MIC.

of patients after 24 h of treatment (7). Similarly, De Waele et al. showed that a fixed loading dose (1,000 g if TBW was <65 kg; 1,500 mg if TBW was ≥65 kg) followed by a CI daily dose of 2,000 mg/24 h was associated with serum drug concentrations of <20 mg/liter for 48% and 39% of patients on days 2 and 3 of treatment, respectively (21). Some authors have, therefore, suggested alternative dosing regimens to rapidly optimize drug concentrations in such patients. In a small study ($n = 20$), Jeurissen et al. showed that a loading dose of 1,000 mg followed by a daily dose of 3,000 mg provided adequate vancomycin concentrations (25 mg/liter) on day 2 of therapy in patients with normal renal function (22). This regimen has never been prospectively validated. In another study, Pea et al. analyzed a cohort of 70 patients treated with CI of vancomycin and proposed two dosing nomograms to achieve drug concentrations of 15 or 20 mg/liter at steady state (48 to 72 h after the onset of treatment) after a loading dose of 15 mg/kg given over 2 h (14). The performance of these formulas was prospectively validated in a similar cohort ($n = 63$) of patients in the same study.

However, optimization of vancomycin regimens should aim to achieve therapeutic concentrations within a few hours of the onset of treatment. With the dosing regimen we tested, we obtained target serum vancomycin concentrations at 12 h of treatment. This was achieved using a higher than recommended loading dose and a daily regimen adjusted to renal function. Similarly, Carricajo et al. reported that a vancomycin regimen based on a loading dose of 30 mg/kg, followed by 30 mg/kg per day in patients with a CrCL of >50 ml/min, enabled minimum concentrations of 20 mg/liter to be attained after 24 h of treatment in 13/22 critically ill patients; all the patients with insufficient serum drug concentrations had CrCLs of >120 ml/min (15). Saugel et al. also reported that the use of a drug regimen based on a loading dose of 20 mg/kg of TBW, followed by a daily regimen ranging from 20 mg/kg (if renal insufficiency) to 30 mg/kg (if no renal insufficiency), was associated with insufficient vancomycin concentrations in <15% of patients ($n = 34$); 36% of patients in this cohort had excessive serum concentrations (23). Thus, an initial loading dose of 30 to 35 mg/kg is necessary to achieve target vancomycin ranges rapidly in critically ill patients. The use of a high loading dose may also explain the high proportion of patients with "excessive" rather than "insufficient" drug concentrations. However, the occurrence of excessive drug concentrations was also lower than in the study by Saugel et al. (23), probably because of a more precise dose adjustment according to different CrCL ranges. The consequences of excessive serum vancomycin concentrations of short duration in critically ill patients need to be explored in order to determine the optimal balance between the advantages of rapid attainment of adequate therapeutic concentrations and the risks of potentially toxic concentrations.

The main risk factors predicting inadequate serum vancomycin concentrations were BMI and CrCL. Although drug CL is almost linearly correlated with CrCL (7), we found more patients with insufficient drug concentrations in the lowest and highest CrCL ranges. This finding is explained mainly by the use of the CG-CrCL, which may largely underestimate residual renal function in critically ill patients with augmented renal clearance or overestimate the degree of acute renal impairment (24). Moreover, some patients have very high renal blood flow and increased drug CL—so-called augmented renal clearance—which has already been reported to be a major determinant of low serum antibiotic concentrations in this patient population (20). Concern-

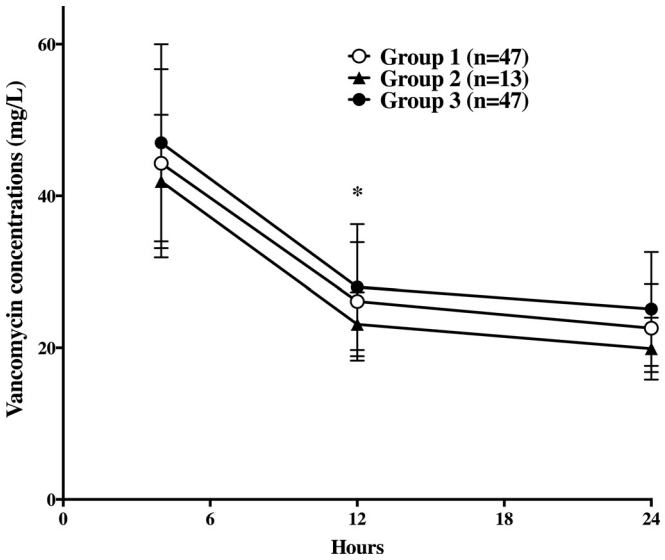

FIG 3 Vancomycin concentrations at different time points in the three groups, according to the differences in creatinine clearances measured using the Cockcroft-Gault formula or daily urinary excretion (see Materials and Methods). Two-way analysis of variance was performed ($P = 0.02$); an asterisk indicates differences at a specific time point according to the Bonferroni *post hoc* analysis.

ing BMI, several studies have suggested that daily vancomycin regimens should be administered according to total body weight (25, 26). However, obese patients are at a high risk of insufficient drug concentrations (27), and the measurement of at least two drug concentrations per day, in order to optimize drug regimens in this setting, has been suggested (26). In our study, low and high BMIs were significantly associated with excessive and insufficient drug concentrations, respectively. However, estimated body weight and height for critically ill patients may be inaccurate by as much as 11 and 15%, respectively (28); weight prediction errors of >20% were observed in almost 20% of cases. This inaccuracy of weight and height estimation by ICU staff may lead to the selection of inappropriate drug regimens for ICU patients; the use of specific scales or beds that can directly measure actual body weight should be considered in order to optimize drug regimens, at least for patients with BMIs markedly outside normal ranges (29). Thus, using these PK parameters, which were prospectively collected, reanalysis of the loading and daily drug doses should be performed in order to understand how to optimize vancomycin regimens in the extreme ranges of weight and drug CL.

The new dosage regimen tested in this study rapidly attained target serum vancomycin concentrations of 20 to 30 mg/liter; however, the pharmacodynamic (PD) index that drives drug effectiveness is the AUC_{0-24}/MIC ratio, in particular when it is >400 (30). As such, CI may achieve target concentrations more rapidly, with a lower daily dose, with more-stable drug concentrations and fewer adverse events, than standard intermittent infusion (5). Although Jeffres et al. showed that serum vancomycin concentrations were significantly correlated to the AUC/MIC ratio, these data were from non-critically ill patients and could not be generalized to patients with severe life-threatening infections (13). In our study, we showed that target concentrations between 20 and 30 mg/liter were appropriate, depending on the likely MIC for the pathogen. Indeed, with strains for which the MIC was ≤1.5 mg/liter, our proposed target concentrations provided adequate AUC/MIC ratios for all patients. Importantly, with pathogens for which the MIC is 2 mg/liter or higher, very high daily regimens and concentrations of vancomycin, which are strongly associated with the development of renal toxicity, would be required (31); thus, other anti-MRSA agents may be preferable in this setting.

There are some limitations to our study. First, we measured the total fraction of vancomycin, which is not predictive of the free concentrations that eventually penetrate tissues and are effective in treating the infectious process (32). However, measurement of free concentrations is not available in daily clinical practice, and PK/PD targets have been defined only on the basis of total concentrations. Second, this new CI regimen may not be applicable to all ICU patients, since we excluded pediatric patients and those undergoing extracorporeal therapies. Also, the presence of more patients with inadequate drug concentrations in the extreme ranges of CrCL would require another PK analysis and regimen adjustment, in particular for those with augmented renal clearance. Moreover, since few obese patients were included, and the proportion of patients with augmented renal clearance was lower than in other studies including critically ill patients (33, 34), more patients with insufficient drug concentrations could be expected if this drug regimen were applied in other settings. This may partly explain why the overall performance of this dosing scheme was better than in earlier studies. Third, we scheduled only three samples to calculate the AUC, which might have been less accurate than if more samples had been obtained. However, this sampling was implemented as the standard of care in our department, and more blood analyses would have been difficult to justify in clinical practice. Fourth, the AUC in the first 24 h may be much higher than on subsequent days due to the administration of the loading dose; thus, target attainment rates on the first day may not reflect the adequacy of the regimen on subsequent days of therapy. Fifth, and finally, the CG-CrCL is a poor predictor of CrCl and antibiotic CL in critically ill patients (24). Unfortunately, the assessment of uCrCl was not the standard of care in our institution at the moment when the study was initiated and could not be implemented for the selection of the initial vancomycin regimen. Monitoring of urinary creatinine excretion over a limited period (e.g., 2 to 4 h) may be a more accurate option for estimating renal function and rapidly guiding the choice of antibiotic regimens in this setting (24, 35).

Conclusions. A new CI dosage regimen for vancomycin enabled rapid attainment of target serum drug concentrations in the majority of critically ill adult patients. To ensure effective dosing, particular attention should be paid to accurate estimations of body weight and to renal clearance, since high BMI and augmented renal clearance are major determinants of drug underdosing.

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F.S.T., F.C., F.J., and J.-L.V. conceived the study protocol. M.H., J.A.R., J.L., J.C., and J.-L.V. participated in the design and coordination of the study. S.C., H.K., and M.B. collected all data. F.S.T. and M.H. supervised data collection. S.C., M.H., H.K., J.A.R., J.L., F.J., J.-L.V., and F.S.T. participated in data interpretation. F.S.T., M.H., M.B., F.J., and J.C. were responsible for drug adaption. J.A.R., H.K., and F.C. carried out the literature search. S.C., J.A.R., and F.S.T. drafted the manuscript; J.L., F.C., F.J., J.-L.V., and J.C. revised the manuscript. All authors read and approved the final version of the manuscript.

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