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# The Effect of Hypoalbuminemia on the Therapeutic Concentration and Dosage of Vancomycin in Critically Ill Septic Patients in Low-Resource Countries

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## Abstract

**Purpose:** To determine whether severe hypoalbuminemia (<25 mg/L) has a significant effect on serum levels of vancomycin and whether it can effect vancomycin dosage regimen and the loading dose administration.

**Material and Methods:** Prospective, cohort, and a single-center study included 61 patients whose vancomycin serum levels were measured in steady state. Vancomycin trough levels ($C_{min}$) that were in the range 15 to 20 μg/mL were considered therapeutic and trough levels higher than 15 μg/mL were considered potentially nephrotoxic.

**Results:** In the group of patients with severe hypoalbuminemia, $C_{min}$ was significantly higher compared to the those with nonsevere hypoalbuminemia (>25 mg/L; 23.04 [19.14] vs 13.28 [11.28], $P = .01$). In the group of patients who received the vancomycin loading dose of 2 g, $C_{min}$ was significantly higher in patients with severe hypoalbuminemia compared to the patients with nonsevere hypoalbuminemia (34.52 [25.93] vs 15.37 [10.48], $P = .04$).

**Conclusion:** In critically ill septic patients with severe hypoalbuminemia, there is a high probability that the loading dose of vancomycin is not necessary since it is associated with potentially toxic vancomycin $C_{min}$, while in the patients with nonsevere hypoalbuminemia the loading dose may be necessary to achieving therapeutic $C_{min}$.

## Keywords

severe hypoalbuminemia, vancomycin, therapeutic drug monitoring, sepsis, critical illness

## Introduction

Treatment of sepsis in critically ill patients represents a big challenge nowadays as most of these patients worldwide come from countries that are underdeveloped or developing. It is believed that 8 million patients die annually of the consequences of sepsis, septic shock, and complications caused by this multiple organ dysfunction syndrome. An additional problem in treatment of these patients lays in the fact that guidelines for sepsis treatments are created in developed countries.[1-4] On the other hand, developing countries have a few adequately functioning medical intensive care units (MICUs) and fully trained critical care specialists, which further aggravates the treatment of septic patients who are critically ill.[5,6] Sepsis and septic shock represent inadequate (too strong) response of the organism to the presence of infection and all guidelines

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advocate that early use of antimicrobials is the cornerstone of sepsis treatment.[7] Adequate dosing of antibiotics is a major challenge, especially in critically ill patients.[8-10] Many factors affect serum drug concentration and consequently the final outcome. Serum albumin levels and renal and hepatic functions significantly affect patient serum levels of antibiotics. Subtherapeutic levels of antibiotics lead to inadequate treatment outcomes and endanger lives of patients, while on the other hand, increase antimicrobial resistance degree.[11] One of antimicrobials frequently used in MICU is vancomycin, a glycopeptide antibiotic that is effective in the treatment of infections caused by gram-positive bacteria. Today, there are protocols that suggest vancomycin dosing for the treatment of critically ill patients and some of them recommend that vancomycin trough serum levels ($C_{min}$) should be in the range of 15 to 20 μg/mL, as well as using the loading dose of 20 to 25 mg/kg to achieve it more rapidly.[12,13] Consulting a clinical pharmacist and introducing therapeutic drug monitoring (TDM) into the everyday practice can improve treatment of critically ill patients in low-resource countries.[14] There are not enough studies reporting on results of TDM of vancomycin or impact of hypoalbuminemia on vancomycin serum levels in critically ill patients treated in developing or underdeveloped countries, where regular TDM of antimicrobials is not implemented. This study was created with aims to determine vancomycin serum concentrations in critically ill patients using standard dosage regimen with the focus on defining the impact of hypoalbuminemia on vancomycin serum levels. Besides this, the impact of implementing a fixed loading dose to vancomycin serum levels was tested.

## Methods

### Study Design

This is a prospective, cohort, and single-center study performed at the Medical Intensive Care Unit of the University Clinical Center of the Republic of Srspka (MICU UCC RS) over a 1-year period. Measurement of $C_{min}$ was performed at the Institute for Laboratory Diagnostics UCC RS. Sampling of biological material from the patients included in the study was approved by the Ethical Committee of the UCC RS.

### Population

The study included 61 patients who were treated at the MICU UCC RS and who met the inclusion criteria.

Patients were eligible for inclusion if they all met the following criteria: (1) age ≥18 years, (2) with severe sepsis (defined as presumed or confirmed infection with new-organ dysfunction in the previous 48 hours), (3) treated by vancomycin for less than 24 hours at the time of assessment, and (4) with an expected ICU stay longer than 72 hours. Patients with end-stage renal disease (estimated glomerular filtration rate <15 mL/min/1.73 $m^2$ itself has been suggested as an endpoint) and/or receiving renal replacement therapy were excluded from the study.

### Study Protocol

Patients were treated with 1 g of vancomycin every 12 hours. A fixed vancomycin loading dose of 2 g was recommended by a clinical pharmacist involved in morning rounds at MICU since it was suitable for most patients. Patients weight cannot be precisely measured at our clinic and average weight of patients according to the anamnestic data was 78.11 kg. Given the fact that the recommended vancomycin loading dose for the treatment of critically ill patients is 25 to 30 mg/kg, the loading dose of 2 g is in the range of 1937 to 2325 g, calculated for the average weight of studied patients (77.5 kg). Physicians treating patients decided on whether vancomycin loading dose should be administered. The following patient data were collected from the medical charts and other medical documentation: diagnosis, comorbidities, serum albumin levels, platelets, serum creatinine, urea, bilirubin, aspartate aminotransferase, alanine aminotransferase, time of blood sampling, and time of vancomycin administration. Cockcroft-Gault formula was used for the estimation of creatinine clearance (CrCL). Sampling of biological material was performed using the following protocol:

1. The first blood sample (3-5 mL) was taken 30 minutes before the fourth dose of vancomycin.
2. The second blood sample (3-5 mL) was taken 1 hour after completion of vancomycin intravenous (IV) infusion.
3. Both samples were sent to the Institute for Laboratory Diagnostics 2 hours after sampling.
4. Samples were preserved at the Institute for Laboratory Diagnostics at the temperature 0°C to 5°C.

It is considered that vancomycin trough serum levels were in the therapeutic range if measured $C_{min}$ value was in the range 15 to 20 μg/mL.

Although there are only few data that show clear connection between vancomycin serum levels and therapeutic efficacy or toxicity, Infection Disease Society of America and American Thoracic Society recommend that therapeutic range for $C_{min}$ is 15 to 20 μg/mL, since it is shown that the range recommended by *Geraci* of 5 to 10 μg/mL cannot achieve area under the curve/minimum inhibitory concentration (AUC/MIC) ≥400, which is necessary for the isolates with MIC ≤1 μg/mL.[15-17]

When it comes to vancomycin toxicity, data are contradictory since some studies show that vancomycin leads to nephrotoxicity after its serum levels are above >10 μg/mL.[18,19] While other authors state that the risk of toxic renal effects is increased with vancomycin serum levels above 15 μg/mL.[20,21] Because of the fact that the serum concentration of vancomycin 15 μg/mL is needed to achieve therapeutic effect and that values over 15 μg/mL can cause nephrotoxicity, TDM of vancomycin is preferred. However, vancomycin TDM is rarely performed on regular basis in developing countries.[22]

### Measurement of Vancomycin Plasma Concentrations

The measurement of vancomycin plasma concentrations was performed using Cobas (*Roche/Hitachi cobas c systems, cobas c* 501), with measuring range of 17 to 80 µg/L (1.2-55.2 µmol/L). The test is based on a homogenous enzyme technique for quantitative analysis of vancomycin in human serum or plasma. The principle of the test involves the competition between the drug in the sample and the drug labeled with the glucose-6-phosphate dehydrogenase (G6PDH) enzyme to bind to the receptor sites on the antibody. Enzyme activity is decreased by binding to the antibody, which allows determination of drug concentration in the sample by measuring enzymatic activity. The active enzyme converts the oxidized nicotine amide dinucleotide (NAD) into NADH, resulting in a change in spectrophotometrically measured absorption. The process is not disturbed by the endogenous G6PDH since the coenzyme reacts only with the bacterial (*Leuconostoc mesenteroides*) enzyme in the assay.

### Statistical Analysis

Results are presented mainly using tables and graphs, and data processing was performed by descriptive and comparative statistical methods. The results are expressed as mean (standard deviation [SD]) for continuous variables and as numbers (percentages) for categorical variables. The data distribution was analyzed by the Kolmogorov-Smirnov test. Comparisons between continuous variables were performed using the Student *t* test or the Mann-Whitney test, and categorical variables were compared using the $\chi^2$ test or the Fisher exact test as appropriate. The *P* value <.05 was considered statistically significant. Statistical analyses were performed using the SPSS 20 statistical program.

## Results

Sixty-one patients were included in the study, of whom 36 (59%) were males, with mean (SD) weight 78.11 (17.63) kg, mean (SD) height 175.07 (8.55) cm, and mean (SD) body mass index (4.29). 25 (41%) patients were older than 65 years, and 29 (47.5%) patients had 1 or more chronic comorbidities. Mean SAPS II score (SD) of studied patients was 64.16 (14.27).

Table 1 shows the results of measured vancomycin $C_{min}$, relative to the serum creatinine concentration, CrCL, sex and age structure, as well as the presence of chronic comorbidity. The mean value (SD) of $C_{min}$ measured in 61 patients included in the study was 17.28 (15.63). Vancomycin $C_{min}$ of 15 µg/mL was considered borderline value for therapeutic efficacy, since it is lower value of vancomycin serum therapeutic range (15-20 µg/mL). Accordingly, patients were divided into 2 groups, patients with $C_{min}$ >15 µg/mL and patients with $C_{min}$ <15 µg/mL. Of the total of 61 patients, 27 (44.3%) patients had $C_{min}$ >15 µg/mL, while 34 (55.7%) patients had $C_{min}$ <15 µg/mL.

Table 2 shows the difference in individual demographic and clinical data in regard to albumin values (cutoff value of

**Table 1.** Vancomycin Trough Concentrations and Renal Function Parameters.

| | | Male | Female | *P* | >65 Years | <65 Years | *P* | With Comorbidities | Without Comorbidities | *P* | PLT >150 | PLT <150 | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N ($C_{min}$, mean [SD], µg/mL) | 61 (17.28 [15.63]) | 36 (15.12 [13.32]) | 25 (20.40 [18.30]) | .196[a] | 25 (23.68 [16.13]) | 36 (12.84 [13.81]) | .007[a] | 29 (18.69 [14.54]) | 32 (16.00 [16.69]) | .508[a] | 40 (15.29 [10.86]) | 18 (21.22 [23.72]) | .194[a] |
| N ($C_{min}$ >15 µg/mL, mean [SD], µg/mL) | 27 (30.47 [14.90]) | 14 (28.05 [12.85]) | 13 (33.08 [16.96]) | .391[a] | 17 (31.08 [14.21]) | 10 (29.44 [16.74]) | .788[a] | 15 (28.66 [13.70]) | 12 (32.74 [16.60]) | .490[a] | 18 (25.99 [5.68]) | 6 (48.99 [22.20]) | <.01[a] |
| N ($C_{min}$ <15 µg/mL, mean [SD], µg/mL) | 34 (6.81 [3.75]) | 22 (6.88 [3.33]) | 12 (6.67 [4.57]) | .876[a] | 8 (7.97 [3.98]) | 26 (6.45 [3.68]) | .326[a] | 14 (8.01 [3.94]) | 20 (5.97 [3.45]) | .119[a] | 22 (6.53 [3.81]) | 12 (7.33 [3.74]) | .561[a] |
| N (SrCr, mean [SD], µmol/L) | 61 (108.41 [75.50]) | 36 (106.22 [66.14]) | 25 (111.56 [88.61]) | .789[a] | 25 (121.96 [68.18]) | 36 (99 [79.76]) | .246[a] | 29 (123 [94.28]) | 32 (95.19 [51.23]) | .152[a] | 40 (92.38 [56.86]) | 18 (146.22 [101.68]) | .012[a] |
| N (CrCL, mean [SD], mL/min) | 61 (85.94 [45.36]) | 36 (94.52 [44.38]) | 25 (73.58 [44.76]) | .076[a] | 25 (59.74 [32.34]) | 36 (104.13 [44.49]) | <.01[a] | 29 (73.27 [35.27]) | 32 (97.41 [50.73]) | .037[a] | 40 (92.38 [44.08]) | 18 (73.47 [46.03]) | .141[a] |

Abbreviations: CrCL, creatinine clearance; PLT, platelets; SD, standard deviation; SrCr, serum creatinine.
[a]Student *t* test.

**Table 2.** Patients' Characteristics, Clinical Data and Vancomycin $C_{min}$ in Regard to Albumin Levels.

| | Albumin >25 mg/L, N = 36 | Albumin <25 mg/L, N = 25 | Difference (*P* Value) |
|---|---|---|---|
| Male[a] | 21 (58.3) | 15 (41.7) | .89[b] |
| Age (years)[c] | 52.64 (18.69) | 63.92 (11.85) | .01[d] |
| Weight (kg)[c] | 77.22 (19.69) | 79.40 (14.46) | .64[d] |
| BMI (kg/m$^2$)[c] | 25.62 (4.35) | 26.08 (4.27) | .68[d] |
| Creatinine clearance (mL/min)[c] | 95.34 (43.14) | 72.39 (45.90) | .05[d] |
| Serum creatinine (μmol/L)[c] | 93.19 (50.25) | 130.32 (98.59) | .05[d] |
| Chronic comorbidities[a] | 13 (44.8) | 16 (55.2) | .03[b] |
| Platelets ($\times 10^9$/L)[c] | 224.60 (125.77) | 215.61 (168.79) | .82[d] |
| AST (IU/L)[c] | 98.77 (201.59) | 56.67 (37.44) | .43[d] |
| ALT (IU/L)[c] | 105.12 (263.78) | 38.71 (24.19) | .33[d] |
| Bilirubin total (μmoL/L)[c] | 19.54 (11.23) | 21.20 (22.50) | .75[d] |
| Bilirubin direct (μmoL/L)[c] | 6.22 (4.53) | 8.70 (11.05) | .36[d] |
| $C_{min}$[c] | 13.28 (11.28) | 23.04 (19.14) | .01[d] |
| $C_{min}$, CrCL >50 mL/min[c] | 10.03 (8.21), (N = 29) | 19.05 (16.59), (N = 15) | .02[d] |
| $C_{min}$, CrCL >50 mL/min, without vancomycin loading dose | 8.93 (7.86), (N = 20) | 18.82 (18.55), (N = 12) | .04[d] |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index.
[a]Number (percentage).
[b]$\chi^2$ test.
[c]Mean (SD).
[d]Student *t* test.

**Table 3.** Vancomycin $C_{min}$ in Regard to Hypoalbuminemia and Loading Dose Administration.

| | Albumin <25 mg/L, Vancomycin Loading Dose | Albumin <25 mg/L, Without Vancomycin Loading Dose | Student *t* Test | Albumin >25 mg/L, Vancomycin Loading Dose | Albumin >25 mg/L, Without Vancomycin Loading Dose | Student *t* Test | Albumin >25 mg/L, Vancomycin Loading Dose | Albumin <25 mg/L, Vancomycin Loading Dose | Student *t* Test |
|---|---|---|---|---|---|---|---|---|---|
| $C_{min}$, mean (SD) | 34.52 (25.93) | 20.17 (16.68) | .14 | 15.37 (10.48) | 12.37 (11.70) | .47 | 15.37 (10.48) | 34.52 (25.93) | .04 |

Abbreviation: SD, standard deviation.

25 mg/L for severe hypoalbuminemia). Groups of patients with severe hypoalbuminemia (<25 mg/L) were significantly older, had significantly lower serum CrCL levels and significantly higher serum creatinine levels. Using the Student *t* test for small independent samples, significantly higher vancomycin $C_{min}$ was found in the group of patients with severe hypoalbuminemia. This difference was retained even after excluding from the analysis patients who had estimated CrCL <50 mL/min, and even after additionally excluding patients who received the loading dose of vancomycin. In this way, the effect of renal function and the vancomycin loading dose on the serum concentration of vancomycin was eliminated.

Table 3 shows the results of comparing vancomycin $C_{min}$ in relation to severe hypoalbuminemia and the loading dose of vancomycin. In the group of patients who received the loading dose, statistically significant difference was detected between patients with severe hypoalbuminemia and patients with non-severe hypoalbuminemia.

Assessing the risk of renal insufficiency in patients with vancomycin $C_{min}$ >15 μg/mL as a borderline trough toxic value, it was found that a relative risk was significantly increased in these patients (odds ratio [OR] = 6.964, 95% confidence interval [CI], 1.921-25.243). Assessing the risk of vancomycin nephrotoxicity in patients with $C_{max}$ >45 μg/mL as a borderline peak toxic value, it was found that the relative risk was significantly increased in these patients (OR = 2.380, 95% CI, 0.720-7.869).

## Discussion

Analyzing the obtained results, it is clear that patients with severe hypoalbuminemia had higher vancomycin $C_{min}$ values, especially those who received the loading dose of vancomycin. In studied patients, severe hypoalbuminemia was associated with age (>65 years), the presence of chronic comorbidity, and higher values of urea and creatinine. In addition to this, it is important to note that in the studied population desired therapeutic vancomycin serum levels (15μg/mL) were achieved in only 27 (44.3%) patients.

Hypoalbuminemia is defined as the serum value of albumin less than 35 mg/L, but severe or clinically significant hypoalbuminemia is characterized with serum albumin lower than 25 mg/L.[23,24] In hypoalbuminemia, which is common in critically ill, there is a possibility of modification of volume of distribution (Vd) and CL of vancomycin, which is in moderately high grade (55%) bounded to albumins.[25] In the present study, all

patients had albumin serum levels less than 35 mg/L, and 41% of them had severe hypoalbuminemia, or serum albumin values less than 25 mg/L.

Comparing mean values of vancomycin $C_{min}$ between the groups of patients with severe hypoalbuminemia and patients with nonsevere hypoalbuminemia, significantly higher value of $C_{min}$ in the group of patients with severe hypoalbuminemia was found ($P = .01$). This difference remains statistically significant even after patients with CrCL <50 mL/min were eliminated from the analysis ($P = .02$). Vancomycin $C_{min}$ values in the group of patients with severe hypoalbuminemia who received the loading dose of vancomycin were significantly higher than the desired serum values of 15 μg/mL.

In patients with severe hypoalbuminemia, vancomycin $C_{min}$ is significantly higher in patients who received the loading dose of vancomycin. Most studies advocate that toxic effect of vancomycin appear when $C_{min}$ levels are above15 μg/mL.[26] The vancomycin loading dose administration in patients with severe hypoalbuminemia can potentiate toxic effects of vancomycin; hence, its use in these groups of patients is questionable. Similar results came from Mizuno et al who showed that severe hypoalbuminemia in patients older than 75 years significantly prolongs vancomycin elimination time ($P = .049$), and it increases the number of patients whose AUC/MIC was higher than 450 μg · h/mL ($P < .001$). Values of $C_{min}$ and $C_{max}$ were higher in patients with severe hypoalbuminemia, but this difference did not reach statistical significance. Besides, in patients who had AUC/MIC higher than 450 μg · h/mL, higher rate of nephrotoxicity was detected ($P < .001$).[24]

The vancomycin loading dose of 25 to 30 mg/kg is recommended for rapid achievement of therapeutic serum concentrations, especially in critically ill patients where increased Vd is expected (sepsis, septic shock, burns, or administration of high volume of IV fluids). After analyzing the results, it becomes clear that the mean value of vancomycin $C_{min}$ in patients with severe hypoalbuminemia who received the vancomycin loading dose is significantly higher than borderline $C_{min}$ for vancomycin toxicity. On the other hand, patients with severe hypoalbuminemia who did not receive the vancomycin loading dose had vancomycin $C_{min}$ values in reference range.

In patients with non-severe hypoalbuminemia, administration of the vancomycin loading dose led to achieving therapeutic serum concentrations of vancomycin in the steady state, while patients who did not receive the vancomycin loading dose had subtherapeutic vancomycin serum concentrations. Since literature data on influence of hypoalbuminemia and the vancomycin loading dose on vancomycin $C_{min}$ in critically ill patients are scarce, comparing results with other studies is not possible.

Analyzing the results of this study, it can be noted that out of 61 patients included in this study, only 27 (44.3%) had vancomycin $C_{min}$ >15 μg/mL, while 34 (55.7%) patients had vancomycin $C_{min}$ <15 μg/mL. Reasons for these results can be found in the fact that small number of patients received the vancomycin loading dose. Similar results were presented by Obara et al who found that only 40% of ICU patients treated with vancomycin reach therapeutic serum concentrations.[27] Reasons for this can be found in the absence of the vancomycin loading dose and the lack of TDM on a regular basis.[28]

Physicians indicated the vancomycin loading dose of 2 g in 16 (26.2%) patients, while it was not indicated in 45 (73.8%) studied patients. Truong et al investigated the influence of the vancomycin loading dose of 2 g and if changing the previous practice in ICU, which meant administering the vancomycin loading dose to patients for whom physicians considered to be necessary (younger patients, complicated disease, patients without renal disease) would more rapidly achieve the therapeutic concentrations of vancomycin in the serum of critically ill patients. It was shown that vancomycin $C_{min}$ was significantly higher in patients who received the vancomycin loading dose (14.9 [6.3] μg/mL vs 9.8 [6.6] μg/mL, $P = .001$). After introducing the practice of administering the vancomycin loading dose in the ICU, 33% therapeutic vancomycin concentrations were reached, compared to only 13% in the previous period.[29] Kitzis and Goldstein presented that administration of the vancomycin loading dose of 15 mg/kg led to significantly higher serum vancomycin concentrations compared to administration of the vancomycin loading dose of 500 mg (19.1 [7.4] μg/mL vs 10.4 [2.7] μg/mL; $P < .001$),[30] while Wang et al showed that administration of the vancomycin loading dose of 25 mg/kg led to therapeutic but potentially toxic vancomycin serum concentrations of 26.4 (9.3) μg/mL, which was detected 1 hour after completing vancomycin infusion.[31,32]

This study was impaired by several limitations. First, the results are extracted from a single-center study conducted in a specific, relatively small population of nonsurgical ICU patients without renal impairment, thus not generalizable to all critical care settings. In addition, variation of pharmacokinetic parameters over time may also have influenced serum vancomycin concentrations over time. Clinical outcomes were not assessed since it was difficult to exclude the influence of many other parameters, and MICUs were not available; hence, we presumed certain serum concentrations of vancomycin to be therapeutic, based on the literature data.

From the results obtained in this study, it can be concluded that in septic, critically ill patients with severe hypoalbuminemia, administration of the vancomycin loading dose can lead to potentially toxic serum concentrations. On the other hand, in patients with nonsevere hypoalbuminemia, the vancomycin loading dose administration led to achieving therapeutic serum concentration of vancomycin. Vancomycin TDM is needed in treatment of critically ill patients in order to achieve optimal treatment goals.

## Declaration of Conflicting Interests

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