


Outcomes and Nephrotoxicity Associated with Vancomycin Treatment in Patients 80 Years and Older

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Purpose: This retrospective observational study investigated the efficacy and safety of vancomycin to treat patients aged 80 years and older. In particular, the associations between vancomycin trough concentration (VTC) and treatment outcomes or nephrotoxicity were explored.

Patients and Methods: Patients aged ≥ 80 years had received ≥ 3 vancomycin treatments and ≥ 1 detection of VTC. Treatment outcomes were defined as success or failure. Nephrotoxicity was considered an increase in serum creatinine ≥ 44.2 mmol/L, or 50% above baseline, for ≥ 2 consecutive days. Univariate and multivariate analyses were performed to identify risk factors for treatment failure and nephrotoxicity.

Results: Of 349 patients, 120 (34.4%) experienced treatment failure. For patients with VTCs at <10 , 10–15, 15–20, and ≥ 20 $\mu\text{g/mL}$, the clinical response rates were, respectively, 77.8, 77.0, 80.5, and 61.0%; the 30-day mortality rates were 2.8, 15.0, 15.3, and 37.8%; and the rates of persistent bacteremia were 16.7, 12.4, 11.9, and 11.0%. The multivariate analysis indicated that blood urea nitrogen ≥ 11 g/dL and heart failure were independently associated with treatment failure; but not VTC ($P = 0.004, 0.016, 0.828$, respectively). During vancomycin treatment, 42 (12.0%) patients experienced nephrotoxicity with recovery time 7.5 ± 4.5 days. Fewer than half of patients with nephrotoxicity recovered after suspending vancomycin application. The variables found independently associated with increased nephrotoxicity were: VTC ≥ 15 $\mu\text{g/mL}$; treatment duration ≥ 15 d; and concomitant aminoglycosides administration ($P = 0.024, 0.035, 0.029$).

Conclusion: In patients aged 80 years and older, elevated VTC level was not associated with favorable treatment outcomes. Patients with VTC ≥ 20 $\mu\text{g/mL}$ appear to suggest a worsened prognosis compared with lower VTCs. The risk of nephrotoxicity increases with elevated VTC, longer treatment time, and concomitant aminoglycoside administration.

Keywords: elderly, vancomycin trough concentration, outcome, nephrotoxicity

Plain Language Summary

Vancomycin is commonly used to treat Gram-positive bacterial infections that resist antibiotics, but can be detrimental to kidney function. We hypothesized that it may be more difficult for very old patients to eliminate vancomycin quickly, which puts their renal system at risk. This study reviewed evidence to analyze the safety and efficacy of vancomycin, in 349 patients aged 80 years or older who had received at least 3 vancomycin treatments to treat recalcitrant bacterial infections of various types. Nephrotoxicity (a poisonous effect on the kidneys) was also measured, based on a certain level of blood serum creatinine lasting at least 2 days. The results showed that bacterial infection was not controlled in about 34% of

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patients, but this lack of improvement was due to factors other than vancomycin (such as heart failure). About 12% experienced nephrotoxicity which was related to the vancomycin treatment, among whom fewer than half recovered, especially those with higher VTC, duration of treatment, and simultaneous use of another antibiotic (aminoglycosides). A favorable clinical response to vancomycin was less likely as VTC increased, and indeed $VTC \geq 20 \mu\text{g/mL}$ indicated a worse prognosis. Therefore, vancomycin should be applied with caution in the elderly. Treatment decisions should consider multiple factors, including a suitably low VTC, to improve vancomycin efficacy and reduce the risk of nephrotoxicity.

Introduction

Vancomycin is a glycopeptide antibiotic with a history that can be traced back to the 1950s when it was discovered produced by *Streptomyces orientalis* in soil.¹ It is one of the most commonly prescribed drugs, and for decades has been the main treatment for patients with suspected or documented antibiotic-resistant Gram-positive infections.^{2–4} The recommended pharmacokinetic-pharmacodynamic target AUC/MIC ratio for vancomycin is >400 (ie, the ratio of the area under the serum concentration time curve [AUC] to the minimum inhibitory concentration [MIC]). This is particularly true for treating methicillin-resistant *Staphylococcus aureus* (MRSA) infections.⁵ To facilitate management and simplify vancomycin dose adjustments and monitoring, multiple organizations in 2009 recommended trough monitoring and maintaining trough concentrations between 15 and 20 $\mu\text{g/mL}$. Since these guidelines were published, several studies have evaluated the efficacy and safety of recommended vancomycin trough concentration (VTC), with conflicting results. More recent research suggested that high VTC did not correlate with any notable improvement in treatment outcomes, in either adults or children.^{6–8}

Nephrotoxicity remains the most severe vancomycin-associated adverse effect, as reported by many studies, and is associated with increased mortality, hospital stay, and medical expense.^{9,10} Although vancomycin is often associated with nephrotoxicity, the direct mechanisms are controversial. Multiple studies have focused on oxidative stress as a potential mechanism of nephrotoxicity, especially involving the proximal tubule.^{11,12} Other studies showed that vancomycin can change the energy-dependent renal reabsorption function of the proximal tubule cells and alter mitochondrial function, which is also associated with vancomycin-induced renal toxicity.¹³

In a meta-analysis, van Hal et al¹⁰ reported a 5% to 43% rate of vancomycin-associated nephrotoxicity. Recently, Sinha Ray and colleagues¹⁴ conducted a meta-analysis comprising 13 studies and showed that the relative risk of nephrotoxicity during vancomycin treatment was 2.45 (OR 2.45; 95% CI 1.69–3.55), and the attributable risk of nephrotoxicity was 59%. Additionally, these studies also showing that higher VTC and longer duration of vancomycin treatment were independent risk factors associated with nephrotoxicity.^{10,14}

Vancomycin is eliminated from the body mainly via the kidneys. The clearance is linearly related to the glomerular filtration rate, and thus reduced renal clearance may lead to increased VTC.¹⁵ Previous studies have showed that longer half-life ($t_{1/2}$), higher volume of distribution and reduced clearance of vancomycin in older patients, compared with the younger, and this may lead to increased VTC level and the risk of nephrotoxicity.^{16–18} It is estimated that by 2050 the percentage of the population older than 65 years will be as high as 40%, and the very old as much as 15%.¹⁹ This demographic change will increase the number of geriatric patients in all areas of medical care. Guidelines regarding renal safety and trough concentration, and whether VTC correlates with risk of nephrotoxicity in elderly patients, are an important concern in clinical practice. This is particularly true for patients aged 80 years and older. However, studies of vancomycin treatment specifically in this group of patients are rare.

The current study investigated the efficacy and safety of vancomycin to treat patients aged 80 years and older. In particular, the associations between VTC and treatment outcomes or nephrotoxicity were explored.

Patients and Methods

Data Collection

This is a retrospective observational study which includes data of patients treated at Beijing Friendship Hospital, Capital Medical University, from January 2017 to December 2019. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (No. 2020-P2-109-01). The committee waived the need for informed consent in this retrospective study with no potential harm to subjects, and permission was granted to use data for analysis and all the data is strictly confidential.

Inpatients who met all the following criteria were included: aged ≥ 80 years; with confirmed or suspected complicated Gram-positive infection; and with at least one detection of serum steady state VTC. Patients who received any of the following were excluded: vancomycin oral or continuous intravenous treatment; < 3 vancomycin doses, with undetectable serum VTC; or renal replacement therapy such as hemodialysis, peritoneal dialysis, or hemofiltration before or during vancomycin treatment. Also excluded were patients with severe chronic renal dysfunction (creatinine clearance ratio < 20 mL/min), or in whom renal injury occurred prior to vancomycin administration (see below); or lacking information to evaluate the treatment effect and nephrotoxicity. Acute kidney injury was defined as an increase in serum creatinine (SCr) level by > 0.3 mg/dL within 48 hours, or an increase in SCr level > 1.5 -fold the baseline, which was known or presumed to have occurred within the preceding 7 days, or urine output < 0.5 mL/kg/h for 6 hours.⁹

The following data were collected from the patients' medical records: demographics (age, gender), body weight and body mass index (BMI), and comorbid disease. Noted infections were: pneumonia, blood stream infection, endocarditis, osteomyelitis, meningitis, urinary infection, biliary system infection, celiac infection, and skin or soft tissue infection. Laboratory data included SCr, blood urea nitrogen (BUN), serum albumin, hemoglobin, and estimated glomerular filtration rate (eGFR). The particulars of vancomycin therapy were dosage, treatment duration, and VTC. Noted etiologies were MRSA, coagulase-negative *Staphylococcus*, *Streptococcus*, *Enterococcus*, and minimum inhibitory concentrations of these bacteria. Drugs that influence renal function were recorded, including aminoglycosides, diuretics, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), cyclooxygenase 2 inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Finally, data regarding nephrotoxicity and treatment outcome were gathered. VTCs were obtained within 72 hours of treatment (before the fourth and fifth vancomycin administration). During vancomycin therapy, the SCr, and VTC were monitored every 3 to 4 days, and endogenous creatinine clearance was tested weekly.

Treatment Outcome Evaluation

Treatment outcomes were classified as either success or failure, based on a composite evaluation of clinical response, persistent bacteremia, and 30-day mortality.

Clinical response was defined as with response or no response, based on infection signs and symptoms, laboratory tests, and medical images. Response was defined as infection signs and symptoms, laboratory tests, and medical images relief or cure after treatment. No response was defined as no improvement in infection signs or symptoms, or worsening or even appearance of new symptoms associated with the original infection. Persistent bacteremia meant lasting at least 7 days after the initial treatment of vancomycin. The 30-day mortality was the mortality rate at 30 days after vancomycin therapy. Treatment success was considered treatment response, microbiological eradication, and survival within 30 days after the initial vancomycin treatment. Conversely, treatment failure was defined as no clinical response, or persistent bacteremia, or death within 30 days after initial vancomycin treatment.^{6,8,20}

Evaluation of Nephrotoxicity

Vancomycin-associated nephrotoxicity was defined as either an increase in SCr ≥ 44.2 mmol/L (0.5 mg/dL), or 50% above baseline, from initiation of vancomycin to 72 hours after completion of therapy, excluding other causes of acute kidney injury.⁸

Statistical Analysis

Patients were classified as vancomycin treatment success or failure, or with or without vancomycin-associated nephrotoxicity, and their demographic and clinical variables compared. Categorical data were analyzed using the chi-squared test or Fisher's exact test, and continuous data were examined using Student's *t*-test or a Mann-Whitney *U*-test for small sample parametric or nonparametric variables. Cox multiple variable regression analyses were performed to identify the risk factors for vancomycin outcome and nephrotoxicity. All variables with a *P*-value < 0.05 in the univariate analysis were included in the final regression model. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software, version 25.0 (SPSS, Chicago, IL, USA).

Results

Demographics and Clinical Characteristics

The study population comprised 349 elderly (≥ 80 years) patients with a median age of 88.0 (84.0, 91.0) years;

71.3% were men (Table 1). More than half (55.7%) had a BMI of 18.5–24.9 kg/m². Most of the patients had at least one comorbidity, including hypertension (71.1%), chronic heart failure (54.4%), diabetes (37.0%), chronic kidney dysfunction (24.1%), malignancies (17.5%), and respiratory diseases (15.2%).

Most of the subjects (97.4%) had only one infection site, while the rest had 2 or more (Table 1). The main infection sites were the respiratory system (80.8%), urinary (8.0%), blood stream (6.3%), biliary system (4.0%), celiac (2.0%), and skin/soft tissue (1.7%). Gram-positive bacteria were detected in the blood or body fluid cultures of 35.5%, including 47, 43, 29, and 2 strains of *Enterococcus*, MRSA, coagulase-negative *Staphylococcus*, and *Streptococcus*, respectively.

Treatment Outcomes

Among the 349 patients, 229 (65.6%) and 120 (34.4%) experienced treatment success and failure, respectively (Table 1). There were significant differences between the success and failure treatment groups only with regard to the following: rate of chronic heart failure ($P = 0.029$), VTC level ($P = 0.012$), vancomycin admission daily dose ($P = 0.045$), estimated glomerular filtration rate (eGFR; $P = 0.049$) and BUN ($P = 0.041$). Thus, these variables were entered into the multivariable logistic regression model (Table 2). Results of the multivariate analysis indicated that average trough concentration (OR 0.948; 95% CI 0.584–1.538; $P = 0.828$) was not significantly associated with treatment failure. Only BUN ≥ 11 g/dL (OR 1.060; 95% CI 1.019–1.103; $P = 0.004$) and heart failure (OR 1.807; 95% CI 1.118–2.922; $P = 0.016$) were independently associated with treatment failure.

To observe whether targeting the recommended higher VTC (15–20 $\mu\text{g/mL}$)⁵ leads to improved vancomycin treatment outcomes, the patients were stratified into 4 groups based on the following VTCs: <10, 10–15, 15–20, and ≥ 20 $\mu\text{g/mL}$. The clinical response rates of these groups were 77.8, 77.0, 80.5, and 61.0% respectively; the 30-day mortality rates were 2.8, 15.0, 15.3, and 37.8%; and the rates of persistent bacteremia were 16.7, 12.4, 11.9, and 11.0% (Figure 1). The treatment outcomes of the groups with VTC <10, 10–15, and 15–20 $\mu\text{g/mL}$ were not significant different ($P = 0.530$) but it was worse in ≥ 20 $\mu\text{g/mL}$ group ($P < 0.000$).

Nephrotoxicity

SCr and eGFR were routinely monitored in all 349 patients during the vancomycin treatment period

(Table 3). Of these, 42 (12.0%) patients experienced nephrotoxicity. Among those with nephrotoxicity, 37 (88.1%) showed a 50% increase in baseline SCr, and 27 (64.3%) with a SCr increase of ≥ 0.5 mg/dL. (There were 22 patients with not only a 50% increase in baseline SCr, but also an SCr increase of ≥ 0.5 mg/dL). The time to nephrotoxicity was 7.5 ± 4.5 days; in 59.5%, nephrotoxicity occurred during the first week of treatment. After suspending vancomycin application, 20 (47.6%) patients with renal dysfunction returned to baseline level.

A positive association was observed between VTC and nephrotoxicity (Figure 2). Nephrotoxicity increased with VTC. The rates of nephrotoxicity were 9.5, 21.4, 28.6, and 40.5% at VTCs at <10, 10–15, 15–20, and ≥ 20 $\mu\text{g/mL}$, respectively ($P = 0.045$). The univariate analysis suggested that the following were associated with vancomycin-related nephrotoxicity: VTC, treatment duration, hemoglobin level, eGFR, and application of aminoglycosides (Table 3).

These variables were introduced into the multivariate logistic regression model (Table 4), and the results indicated that VTC ≥ 15 $\mu\text{g/mL}$ (OR 2.469; 95% CI 1.127–5.408; $P = 0.024$), treatment duration ≥ 15 d (OR 3.241; 95% CI 1.086–9.672; $P = 0.035$), and concomitant aminoglycosides (OR 5.147; 95% CI 1.187–22.314; $P = 0.029$) were independently associated with increased nephrotoxicity during treatment with vancomycin.

Discussion

The present study evaluated the treatment outcomes and nephrotoxicity of patients aged 80 or more years, with common characteristics such as multiple comorbidities and varying degrees of renal dysfunction. Among the 349 patients enrolled, vancomycin therapy failed for 120 (34.4%), and 42 (12.0%) suffered nephrotoxicity associated with vancomycin. Higher levels of VTC were not associated with better treatment outcomes and did increase the risk of vancomycin-induced nephrotoxicity. In contrast, patients with too high VTC (≥ 20 $\mu\text{g/mL}$) seems have lower clinical response, and highest 30-day mortality rate.

The vancomycin therapeutic guidelines published in 2009 recommended targeting VTC to above 10 $\mu\text{g/mL}$ to prevent drug-resistance and maintaining VTC at 15 to 20 $\mu\text{g/mL}$ for complicated infections to improve vancomycin efficacy.⁵ However, the present study found that higher VTC levels did not correlate with any notable improvement in treatment outcomes. Rather, a VTC higher than 20 $\mu\text{g/mL}$ was associated with worse prognosis.

Table I Demographics and Clinical Characteristics of the Study Population^a

	Total	Vancomycin Treatment		
		Success	Failure	P
Subjects, n	349	229	120	
Age, y, M (Q1, Q3)	88.0 (84.0, 91.0)	88.0 (84.0, 91.0)	88.0 (85.0, 91.0)	0.732
Male, n (%)	249 (71.3)	168 (73.4)	81 (67.5)	0.250
Weight, kg ^b	61.0 (50.0, 70.0)	60.0 (50.0, 70.0)	62.4 (54.3, 70.0)	0.771
Weight, kg, n (%)				0.180
<55	103 (35.9)	73 (38.2)	30 (31.3)	0.245
55–65	82 (28.6)	48 (25.1)	34 (35.4)	0.069
≥65	102 (35.5)	70 (36.6)	32 (33.3)	0.580
BMI, kg/m ²	22.4 ± 3.9	22.3 ± 4.1	22.5 ± 3.7	0.656
BMI, kg/m ² , n (%)				0.414
<18.5	49 (17.1)	36 (18.8)	13 (13.5)	0.260
18.5–24.9	160 (55.7)	101 (52.9)	59 (61.5)	0.732
25.0–29.9	72 (25.1)	49 (25.7)	23 (24.0)	0.754
≥30.0	6 (2.1)	5 (2.6)	1 (1.0)	0.658
Comorbid conditions ^c , n (%)				0.284
Chronic pulmonary disease	53 (15.2)	35 (15.3)	18 (15.0)	0.944
Hypertension	248 (71.1)	167 (72.9)	81 (67.5)	0.288
Heart failure	190 (54.4)	115 (50.2)	75 (62.5)	0.029
Type 2 diabetes	129 (37.0)	84 (36.7)	45 (37.5)	0.880
CKD	84 (24.1)	46 (20.1)	38 (31.7)	0.016
Malignancies	61 (17.5)	35 (15.3)	26 (21.7)	0.136
Infection site ^d , n (%)				0.169
Nosocomial pneumonia	282 (80.8)	186 (81.2)	96 (80.0)	0.783
Blood stream infection	22 (6.3)	11 (4.8)	11 (9.2)	0.111
Endocarditis	Nil	Nil	Nil	—
Osteomyelitis	Nil	Nil	Nil	—
Meningitis	Nil	Nil	Nil	—
Urinary	28 (8.0)	14 (6.1)	14 (11.7)	0.070
Biliary system	14 (4.0)	12 (5.2)	2 (1.7)	0.106
Celiac	7 (2.0)	5 (2.2)	2 (1.7)	0.744
Skin/soft tissue	6 (1.7)	4 (1.7)	2 (1.7)	0.956
Bacterial strains, n (%)				0.620
MRSA	43 (12.3)	20 (8.7)	23 (19.2)	0.055
CNS	29 (8.3)	18 (7.9)	11 (9.2)	0.675
<i>Streptococcus</i>	2 (0.6)	1 (0.4)	1 (0.8)	0.650
<i>Enterococcus</i>	47 (13.5)	26 (11.4)	21 (17.5)	0.110
VTC, µg/mL, M (min, max)	17.0 (4.2, 62.5)	16.5 (4.2, 53.6)	18.1 (6.7, 62.5)	0.035
VTC, µg/mL, n (%)				0.012
<10	36 (10.3)	23 (10.0)	13 (10.8)	0.818
10–15	113 (32.4)	77 (33.6)	36 (30.0)	0.492
15–20	118 (33.8)	86 (37.6)	32 (26.7)	0.041
≥20	82 (23.5)	43 (18.8)	39 (32.5)	0.004

(Continued)

Table 1 (Continued).

	Total	Vancomycin Treatment		
		Success	Failure	P
Vancomycin dose, g/d, n (%)				0.045
<1.5	247 (70.8)	154 (67.2)	93 (77.5)	
≥1.5	102 (29.2)	75 (32.8)	27 (22.5)	
SCr, g/dL, M (Q1, Q3)	67.0 (54.0, 91.4)	65.7 (54.0, 85.7)	72.7 (53.1, 97.1)	0.219
eGFR, mL/min/1.73 m ² , n (%)				0.049
≥90	81 (23.2)	50 (21.8)	31 (25.8)	0.401
60–89	201 (57.6)	142 (62.0)	59 (49.2)	0.021
20–59	67 (19.2)	37 (16.2)	30 (25.0)	0.046
BUN, g/dL, n (%)				0.041
<11	272 (77.9)	186 (81.2)	86 (71.7)	
≥11	77 (22.1)	43 (18.8)	34 (28.3)	
Albumin, g/L	30.9 ± 4.4	31.2 ± 4.4	30.6 ± 4.5	0.223
Hemoglobin, g/dL, M (Q1, Q3)	101.0 (90.0, 119.0)	102.0 (91.0, 121.0)	100.0 (86.3, 115.7)	0.069

Notes: ^aShown as n (%), unless indicated otherwise; ^bbody weight was not available for 38 patients in success group and 24 in failed group; ^cOne patient may have more than one comorbid disease; ^dOne patient may have more than one underlying infection site and/or more than one indication.

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; CNS, coagulase negative staphylococcus; eGFR, estimated glomerular filtration rate; MRSA, methicillin-resistant *Staphylococcus aureus*; VTC, vancomycin trough concentration.

Indeed, recent studies regarding the association between VTC and treatment outcomes are inconsistent. Huang et al²¹ reported that in 50 patients aged at least 80 years, the clinical efficacy of vancomycin treatment was 74.0%, and there was no significant difference in rates of success or failure between groups above or below 15 µg/mL VTC. The results of Hermesen et al²² were similar for patients treated for MRSA infections. Furthermore, a meta-analysis (4 prospective and 12 retrospective cohort studies) found no significant benefit in mortality or treatment outcomes for VTCs ≥15 mg/L relative to lower levels, although the microbiologic control rate was

higher.²³ Another meta-analysis involving patients with MRSA infections found no differences in outcomes or mortality at the same VTC cutoff.²⁴

In contrast, Kullar et al²⁵ found that VTC <15 µg/mL was an independent predictor of treatment failure in 320 patients with MRSA infections, and Cheong et al²⁶ showed a significant association between VTC and response to treatment, also of MRSA infections. In the latter, the VTC was higher in responders (11.64 ± 1.50 µg/mL) than non-responders (9.25 ± 1.59 µg/mL; *P* = 0.036).²⁶ Wei et al⁶ reported that admission to the intensive care unit was associated with vancomycin treatment

Table 2 Multivariate Logistic Regression Analysis of Factors Associated with Vancomycin Treatment Outcomes

	β	SE	OR (95% CI)	P
VTC (µg/mL) ^a	−0.054	0.247	0.948 (0.584–1.538)	0.828
Daily dose, g/d ^b	0.510	0.275	1.665 (0.972–2.852)	0.063
Heart failure ^c	0.592	0.245	1.807 (1.118–2.922)	0.016
BUN, g/dL ^d	0.059	0.020	1.060 (1.019–1.103)	0.004
eGFR, mL/min/1.73 m ² , n (%)				
Reference, ≥90	—	—	—	—
60–90	0.397	0.384	1.487 (0.700–3.158)	0.302
20–60	−0.340	0.316	0.712 (0.383–1.323)	0.283

Notes: ^aVTC was categorized as <15 µg/mL and ≥15 µg/mL; ^bDaily dose was categorized as <1.5 g/d or ≥1.5 g/d; ^cHeart failure was categorized as with or without; ^dBUN was categorized as <11 g/dL and ≥11 g/dL.

Abbreviations: β, regression coefficient; BUN, blood urea nitrogen; CI, confidence interval; OR, odds ratio; SE, standard error; VTC, vancomycin trough concentration.

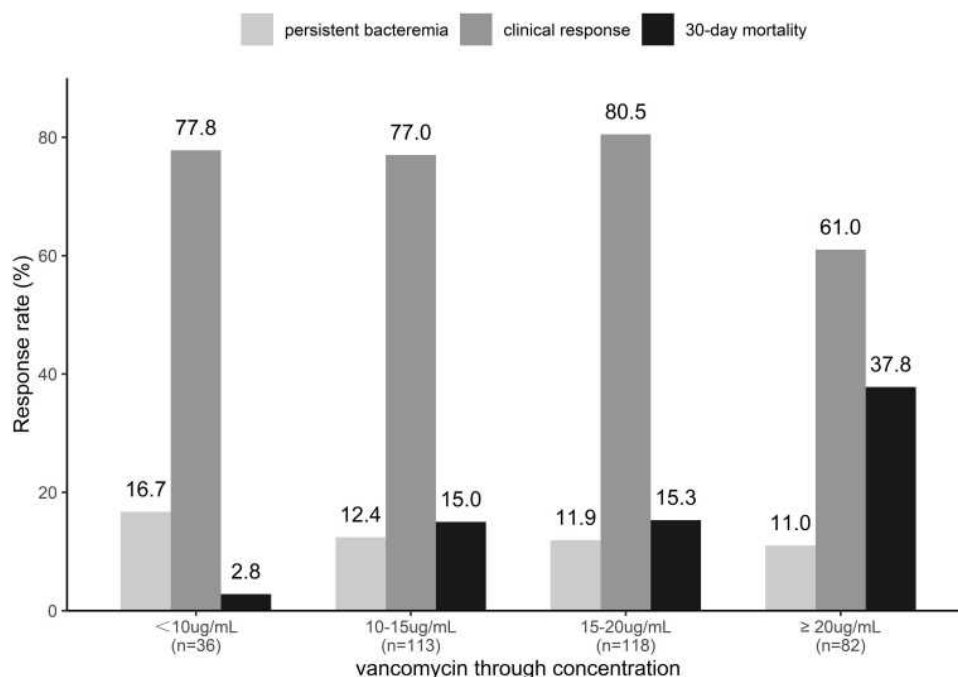


Figure 1 Treatment outcomes of the groups with VTCs <10, 10–15, 10–20 and ≥20 µg/mL.

failure in patients with MRSA infections (OR, 3808; 95% CI 1714–8465; $P = 0.001$). Moore et al²⁷ showed that the APACHE II (Acute Physiology and Chronic Health Evaluation II) score was important in predicting vancomycin failure. In addition, other studies of vancomycin treatment outcomes showed that disease state and infection site, such as pneumonia and endocarditis, were predictors of vancomycin failure.²⁸ Our study showed that concomitant with heart failure and blood urea nitrogen ≥11 g/dL were independent predictors of vancomycin treatment failure in very old patients. One of the potential explanations is that the patients concomitant with chronic heart failure or elevated blood urea nitrogen (≥11 g/dL) were at higher risk of exacerbation of heart failure or occurrence of acute kidney injury (AKI) or renal failure, or even occurrence of multiorgan failure, and thus were associated with vancomycin treatment failure. To the best of our knowledge, no similar findings were reported in other studies, so it needs to be further verified by prospective, large sample studies.

Although the outcomes of the guideline-recommended trough levels for suspected or documented Gram-positive infections remain controversial, there is a much stronger association between higher VTC and nephrotoxicity.^{9,11,29} Lodise et al³⁰ investigated VTC and nephrotoxicity based on pharmacokinetic characteristics and reported that nephrotoxicity increased significantly, by 21 to 33%, for

VTCs of 10–20 and >20 µg/mL, but reduced to 5% when VTC was <10 µg/mL. Similar results were reported by Chuma et al,³¹ the rate of vancomycin-associated nephrotoxicity in patients with initial trough levels ≥20 µg/mL (31.3%) was significantly higher than that of patients with initial trough levels <10 µg/mL (6.3%). Moreover, a study by Pan et al³² of patients aged ≥60 years found that VTC ≥20 µg/mL was an independent risk factor for vancomycin-associated nephrotoxicity and led to a 3-fold increased risk of nephrotoxicity. The present study is consistent with the clinical studies described above. At each higher VTC level (<10, 10–15, 15–20, and ≥20 µg/mL), the rates of nephrotoxicity also rose. VTC ≥15 µg/mL was an independent risk factor for nephrotoxicity, with a 2.46-fold increased risk of nephrotoxicity relative to the lower VTC levels. Thus, nephrotoxicity was closely related to the VTC in our elderly patients.

A meta-analysis of 15 studies compared patients with VTCs less or greater than 15 µg/mL, and found that nephrotoxicity occurred 4 to 17 days after the start of vancomycin application.^{2,9,14,20,33} Another study by Hirai et al³⁴ showed that the mean onset of vancomycin-associated nephrotoxicity was 6.9 ± 4.9 days, and 40.0% of patients recovered from it. Because of large interindividual variability of pharmacokinetic parameters of vancomycin in very old patients, vancomycin levels and

Table 3 Analysis of Nephrotoxicity in Patients with Vancomycin Treatment^a

	Nephrotoxicity			
	Entire Group	Yes	No	P
Subjects, n	349	42	307	
Age, y, M (Q1, Q3)	88.0 (84.0, 91.0)	87.0 (83.7, 91.0)	88.0 (84.0, 91.0)	0.254
Male, n (%)	249 (71.3)	30 (71.4)	219 (71.3)	0.990
Weight [kg, M (Q1, Q3)]	61.0 (50.0, 70.0)			
Weight, kg, n (%)				0.558
<55	103 (35.9)	10 (30.3)	93 (36.6)	0.477
55–65	82 (28.6)	12 (36.4)	70 (27.6)	0.293
≥ 65	102 (35.5)	11 (33.3)	91 (35.8)	0.778
BMI, kg/m ²	22.4 ± 4.0	22.4 ± 3.9	22.2 ± 4.5	0.765
Comorbid conditions ^b , n (%)				0.438
Chronic pulmonary disease	53 (15.2)	6 (14.3)	47 (15.3)	0.862
Hypertension	248 (71.1)	31 (73.8)	217 (70.7)	0.675
Heart failure	190 (54.4)	24 (57.1)	166 (54.1)	0.708
Type 2 diabetes	129 (37.0)	17 (40.5)	112 (36.5)	0.615
Malignancy	61 (17.5)	13 (31.0)	48 (15.6)	0.014
VTC, µg/mL	17.0 ± 7.1	21.1 ± 11.6	16.5 ± 6.1	<0.001
VTC, µg/mL, n (%)				0.045
<10	36 (10.3)	4 (9.5)	32 (10.4)	0.857
10–15	113 (32.4)	9 (21.4)	104 (33.9)	0.106
15–20	118 (33.8)	12 (28.6)	106 (34.5)	0.444
≥20	82 (23.5)	17 (40.5)	65 (21.2)	0.006
Vancomycin dose, g/d, n (%)				0.434
<1.5	248 (71.7)	32 (76.2)	216 (70.4)	
≥1.5	101 (28.9)	21 (23.8)	193 (29.6)	
Treatment duration, d, M (Q1, Q3)	12.0 (7.0, 14.0)	9 (6, 14)	12 (7, 14)	0.045
Treatment duration, d, n (%)				0.182
≤7	95 (27.2)	16 (38.1)	79 (25.7)	0.091
8–14	178 (51.0)	20 (47.6)	158 (51.5)	0.640
≥15	76 (21.8)	6 (14.3)	70 (22.8)	0.210
Time to nephrotoxicity, d, n (%)				—
≤7	25 (59.5)	25 (59.5)	Nil	—
8–14	13 (31.0)	13 (31.0)	Nil	—
≥15	4 (9.5)	4 (9.5)	Nil	—
Renal function changes after vancomycin suspend				
Recover	20 (47.6)	20 (47.6)	Nil	—
Time to recover, d, M (Q1, Q3)	5.0 (4.0, 11.0)	5.0 (4.0, 11.0)	—	—
Albumin, g/L	30.9 ± 4.4	30.7 ± 4.7	31.0 ± 4.4	0.363
Hemoglobin, g/L, M (Q1, Q3)	101.0 (90.0, 119.0)	94.5 (80.0, 105.2)	102.0 (91.0, 120.0)	0.002
<120	263 (75.4)	37 (88.1)	226 (73.6)	
≥120	86 (24.6)	5 (11.9)	81 (26.4)	
BUN, g/dL	8.9 ± 6.6	7.1 ± 1.1	8.8 ± 6.5	0.673

(Continued)

Table 3 (Continued).

	Nephrotoxicity			
	Entire Group	Yes	No	P
SCr, g/dL, M (Q1, Q3)				
Baseline ^c	67.0 (54.0, 91.4)	56.5 (47.3, 89.9)	67.8 (54.7, 91.7)	0.094
End of therapy ^d	68.3 (52.7, 93.3)	128.6 (87.6, 183.1)	65.0 (51.0, 86.4)	0.002
SCr increase ≥ 0.5 mg/dL	27 (7.7)	27 (64.3)	Nil	<0.001
SCr increase from baseline >50%	37 (10.6)	37 (88.1)	Nil	<0.001
eGFR, mL/min/1.73 m ² , n (%)				
≥ 90	81 (23.2)	18 (42.9)	63 (20.5)	0.002
60–89	201 (57.6)	15 (35.7)	186 (60.6)	0.002
20–59	67 (19.2)	9 (21.4)	58 (18.9)	0.696
Concomitant drugs ^e , n (%)				
Aminoglycosides	17 (5.0)	5 (12.2)	12 (4.1)	0.236
Diuretics	77 (22.1)	9 (21.4)	68 (22.1)	0.916
NSAIDs	4 (1.1)	Nil	4 (1.3)	0.457
ACEI/ARB	35 (10.0)	5 (11.9)	30 (9.8)	0.666

Notes: ^aShown as n (%), unless indicated otherwise; ^bOne patient may have more than one comorbid disease; ^cData collected at initiation of vancomycin treatment; ^dData collected within 72 hours after vancomycin therapy completed; ^eFour people used more than one drug to reduce renal perfusion simultaneously: 2 patients with aminoglycosides and diuretics, one patient with aminoglycosides and NSAIDs, and one patient with diuretics and NSAIDs.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; VTC, vancomycin trough concentration.

AUC/MIC index have been documented significantly higher in this particular population in some studies. Elevated vancomycin levels and AUC/MIC index increase the risk of nephrotoxicity.³⁵ Vancomycin-associated nephrotoxicity is usually reversible, with a low incidence of residual damage if the vancomycin is withdrawn in

time or doses are appropriately adjusted after renal damage occurs. According to a literature review by Elyasi et al,¹ 44 to 75% of patients with nephrotoxicity recovered within one week after vancomycin was discontinued. However, some studies indicated that not all critically ill patients could fully recover from vancomycin-

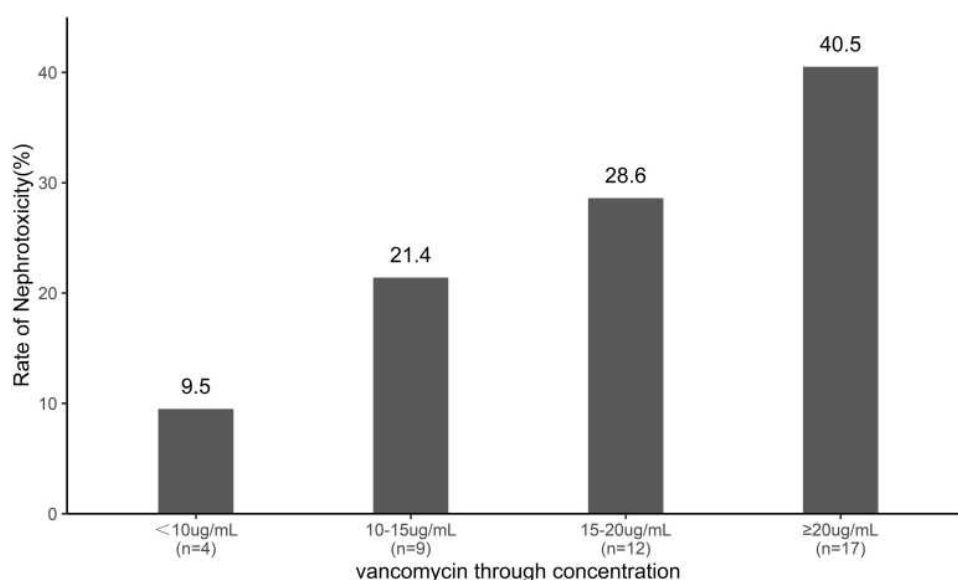
**Figure 2** Rates of nephrotoxicity at VTCs <10, 10–15, 15–20, and ≥ 20 μ g/mL.

Table 4 Multivariate Logistic Analysis for Nephrotoxicity in Elderly Patients on Vancomycin Therapy

	β	SE	OR (95% CI)	P value
VTC ^a , $\mu\text{g/mL}$	0.904	0.400	2.469 (1.127–5.408)	0.024
Aminoglycosides ^b	1.638	0.748	5.147 (1.187–22.314)	0.029
Malignancies ^c	0.560	0.402	1.750 (0.795–3.852)	0.164
Hemoglobin ^d	−0.674	0.515	0.510 (0.186–1.398)	0.190
eGFR, mL/min/1.73 m^2				
Reference, ≥ 90	—	—	—	—
60–90	−0.438	0.468	0.646 (0.258–1.617)	0.350
20–60	0.929	0.500	2.533 (0.950–6.752)	0.063
Treatment duration ^d				
Reference, ≤ 7	—	—	—	—
8–14	0.458	0.517	1.581 (0.574–4.350)	0.376
≥ 15	1.176	0.558	3.241 (1.086–9.672)	0.035

Notes: ^aVTC was categorized as $<15 \mu\text{g/mL}$ and $\geq 15 \mu\text{g/mL}$; ^bAminoglycoside administration was categorized as with or without; ^cMalignancies consisted of solid and blood system tumors, categorized as with or without; ^dHemoglobin was continuous variable.

Abbreviations: β , regression coefficient; CI, confidence interval; OR, odds ratio; SE, standard error; VTC, vancomycin trough concentration.

associated nephrotoxicity, and even mild kidney injury could increase the hospital stay, healthcare costs, and mortality.^{33,36,37}

In the present study, the time to nephrotoxicity was 7.5 ± 4.5 days, and only 20 (47.6%) of these elderly patients recovered after vancomycin was ended. The median time to recovery was 5 days (range, 4 to 11 d). Some studies found no significant relation of nephrotoxicity to vancomycin treatment duration,¹¹ but more often a positive result was found. Study by Hall et al showed that vancomycin duration greater than 15 days was an independent predictor of nephrotoxicity, with a 3.36-fold increased risk of nephrotoxicity relative to patients with shorter treatment duration.³⁸ Another study conducted by Jeffres et al indicated that patients with longer than 14 days vancomycin treatment are more likely to developed renal toxicity (45.0% vs 20.4%; $P = 0.011$).³⁹ Consistent with their finding, our study also showed that prolonged vancomycin treatment duration (≥ 15 days) was independent association with increased nephrotoxicity. This suggests that it is not only the critically ill who may not recover renal function after vancomycin-associated nephrotoxicity, but also the very old. Vancomycin should be applied with caution and attentive monitoring.

In addition to VTC, the univariate analysis also showed that aminoglycosides administered concomitantly with vancomycin was associated with a 4.3-fold greater risk of nephrotoxicity. Cano et al⁴⁰ reported that this risk was 2.6-fold, after adjusting for potential confounders. Other studies also showed a positive association between

concomitant aminoglycosides and vancomycin and nephrotoxicity in elderly patients.^{29,41,42} Besides aminoglycosides, other studies also indicated that concomitant use of renal hypoperfusion medications such as loop/thiazide diuretics,³⁴ ACEI/ARBs,⁴³ NSAIDs⁴⁴ and potential toxins include amphotericin B, trimethoprim-sulfamethoxazole, acyclovir and calcineurin inhibitors may increase the risk of nephrotoxicity, but these results were controversial.^{1,11} However, due to limited data in our study, not all the above agents were included in our analysis, and no statistical significance was found between some renal hypoperfusion medications or potential toxins and nephrotoxicity, except for aminoglycosides. The mechanism of nephrotoxicity when using vancomycin concomitant with aminoglycosides remains uncertain. Some preclinical studies and human data support the potential synergistic nephrotoxicity of vancomycin and aminoglycosides,⁴⁵ but whether the enhanced rate of nephrotoxicity reported with vancomycin use in combination with aminoglycosides is the result of severity of underlying illness, the nephrotoxicity of aminoglycosides itself is not clearly.¹¹ Therefore, in very old patients, multiple factors should be considered when making treatment decisions to improve vancomycin efficacy and reduce the risk of nephrotoxicity.

Three limitations should be noted. This was a single-center retrospective observational study, and prospective and multicenter studies are needed to confirm the findings. Secondly, this analysis did not include factors that may affect the prognosis of elderly patients with infection, such as APACHE II score and frailty. Finally,

because of the small number of patients, a sub-group analysis of the effect of body mass index was not performed.

Conclusion

Regarding vancomycin treatment in the very old, this study found that nephrotoxicity, but not improved outcomes, were associated with elevated VTC, and VTC ≥ 20 $\mu\text{g/mL}$ appears to suggest a worsened prognosis. Vancomycin treatment is likely to fail in the presence of increased BUN and heart failure. Risk factors of nephrotoxicity include higher VTC, prolonged treatment, and concomitant administration of aminoglycosides.

Abbreviations

ACEI, angiotensin converting enzyme inhibitor; APACHE II, Acute Physiology and Chronic Health Evaluation II; ARB, angiotensin receptor blocker; β , regression coefficient; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; CNS, coagulase negative staphylococcus; eGFR, estimated glomerular filtration rate; OR, odds ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; NSAID, nonsteroidal anti-inflammatory drug; SCr, serum creatinine; SE, standard error; VTC, vancomycin trough concentration.

Data Sharing Statement

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

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