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Original Article

Efficacy of Vancomycin on Gram-Positive Bacterial Infection in Elderly Critical Patients and Risk Factors Associated With Nephrotoxicity

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Abstract

Background: Vancomycin is widely used for infections caused by gram-positive bacteria, but little attention has been paid to vancomycin in the treatment of critically ill patients aged ≥80 years. The aim of the current study was to investigate the efficacy of vancomycin and risk factors associated with nephrotoxicity of vancomycin in elderly critically ill patients.

Methods: A retrospective study was performed in a 14-bed medical-surgical geriatric ICU between January 2007 and June 2014. The patients (aged ≥80 years) were included if they received ≥4 doses of vancomycin and the therapy duration was ≥ 2 hours.

Results: The clinical efficacy was 74.0% (37/50). The 28-day mortality was 26.0% (13/50). Of the patients, 24% (12/50) had nephrotoxicity during vancomycin treatment period. The clinical efficacy was 60%, 86.7%, 58.3%, and 33.3%, and the 28-day mortality rate was 20%, 23.3%, 33.3%, and 33.3%, respectively, when the trough concentrations were ≤10 μg/mL, 10–15 μg/mL, 15–20 μg/mL, and ≥20 μg/mL. The multivariate logistic regression analysis showed that an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥25 points, vancomycin trough concentrations ≥15 μg/mL, and the combined use of diuretics (furosemide ≥40 mg/d) were independent risk factors leading to nephrotoxicity.

Conclusion: We did not find that higher vancomycin trough concentrations lead to better clinical outcomes in elderly critically ill patients. Increased vancomycin trough concentrations, high APACHE II scores, and the combined use of diuretics may increase the risks of nephrotoxicity in elderly critically ill patients.

Keywords: Critically ill, Elderly, Nephrotoxicity, Trough concentrations, Vancomycin

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Introduction

Vancomycin is widely used for infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), and *Enterococcus*.[1] In recent years, there has been an increasing number of patients suffering from sepsis or severe infections in the lungs and abdomen caused by gram-positive cocci such as MRSA, MRSE, and *Enterococcus*.[2] Specifically, elderly patients who suffer from severe infections, receive more antibiotics due to their compromised immune function and underlying diseases.[3] Although new antibacterial drugs such as linezolid, daptomycin, telavancin and cephalosporins have been applied for the clinical treatment of MRSA infections,[4] they are only approved for use in limited clinical indications, and none can replace vancomycin in the treatment of MRSA infections as a first-line agent.[5] However, vancomycin has a narrow therapeutic range and can cause several adverse effects including fever, chills, phlebitis, allergic reactions, nephrotoxicity, and neutropenia.[6,7] In response to increasing concerns regarding the efficacy of vancomycin, consensus guidelines for more aggressive dosing and therapeutic drug monitoring were published in 2009. The recommendations, primarily based on *in vitro* and retrospective pharmacodynamic studies, include maintaining vancomycin serum trough levels above 10 μg/mL to avoid the development of resistance, or between 15 and 20 μg/mL for complicated infections.[8] Following the latest recommendation of the Infectious Diseases Society of America to target higher serum vancomycin levels, several groups in the US reported an increase in the rate of nephrotoxicity from 12% to 43%.[9-13] Recently, Hanrahan et al[14] reported nephrotoxicity in 20% of 1430 critically ill patients. Additionally, higher serum vancomycin concentrations and longer treatment duration were independently associated with higher odds of nephrotoxicity. In elderly individuals, renal clearance is significantly reduced.[15] Because vancomycin is eliminated from the body mainly via the kidneys, reduced renal clearance leads to increased vancomycin trough

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concentrations, which may result in nephrotoxicity.[16] However, it is uncertain whether targeting higher blood concentrations leads to an increased efficacy of vancomycin and/or risk of nephrotoxicity in elderly critically ill patients.

The current study was conducted to identify the efficacy and nephrotoxicity of vancomycin in elderly critically ill patients and to explore several high-risk factors (such as age, APACHE II score, serum creatinine before treatment, creatinine clearance rate before treatment, vancomycin trough concentration, course of treatment, concomitant use of nephrotoxic agents, combined use of vasopressor drugs or fuosemide) inducing nephrotoxicity in elderly critically ill patients when treated with vancomycin.

Materials and Methods

Subjects and Data Collection

We performed a single-centre, observational, retrospective study in our 14-bed medical-surgical geriatric ICU between January 2007 and June 2014. Inclusion criteria were age ≥80 years, receiving vancomycin by intermittent infusion, intravenous vancomycin therapy for at least 4 doses, and the course of vancomycin treatment more than 72 hours. Patients who had haemodialysis and did not have regular monitoring of vancomycin concentrations were excluded. These patients were treated with vancomycin as part of their primary antibiotic management of a suspected or proven gram-positive infection.

The medical records of the study population were analysed retrospectively. For each patient, the following data were collected: demographics; 28-day mortality; type of infection and microbiological data; co-morbidities; the Acute Physiology and Chronic Health Evaluation (APACHE) II score;[17] previous and concomitant antimicrobial treatment; use of vasopressor agents and diuretics; use of angiotensin converting enzyme inhibitors (ACEIs) /angiotensin receptor blockers (ARBs), cyclooxygenase (COX)-2 inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs); duration of vancomycin therapy; and clinical outcome. The following laboratory findings before, during and after treatment were collected: haematologic properties (white blood cell count, haemoglobin, and platelet count), routine biochemical tests, C-reactive protein (CRP), and hepatic and renal function tests. The results of bacterial culture, smear, susceptibility tests, and radiology imaging were also collected.

Vancomycin Administration and Monitoring Regime

The initial daily dose of vancomycin was determined based on the creatinine clearance rate (Ccr) in patients using the formula of 15 × Ccr/d (mg).[18] The daily dose was administered by intermittent infusion. Trough serum concentrations were obtained within 72 hours of commencing therapy, after administering a minimum of three doses.[8] The target concentrations were 10-15μg/mL in bloodstream infections and 15-20μg/mL in other types of infections.[10,18] During vancomycin therapy, serum creatinine (Scr) and vancomycin trough concentrations were monitored every 3-4 days, and Ccr was tested weekly. The Ccr was calculated using the following formula: urinary creatinine (μmol/L) × 24 h urine volume (ml)/(1440× Scr (μmol/L)).[19]

Evaluation of Nephrotoxicity

The occurrence of nephrotoxicity was defined as an increase in Scr levels of 44.2 μmol/L or a 50% increase, whichever was greater, on at least 2 consecutive days during the period from initiation of vancomycin therapy to 72 hours after the completion of therapy.[13]

Outcome Evaluation

The clinical outcomes included clinical efficacy and 28-day mortality. The response to vancomycin therapy was classified as vancomycin success and vancomycin failure. Vancomycin success was defined as either the resolution or reduction of the majority of signs and symptoms related to the original infection. Failure was defined as no resolution or reduction of the majority of the signs and symptoms, worsening of one or more signs and symptoms, or the appearance of new symptoms or signs associated with the original infection or a new infection. Clinical efficacy was defined as the rate of vancomycin success. The 28-day mortality was the mortality rate at 28 days after vancomycin therapy.

The microbiological response was classified as eradication, persistence, or eradication with reinfection. The microbiological success rate was defined as the number of patients with eradication divided by the total number of patients with gram-positive pathogens isolated at baseline.

Statistical Analysis

All data were analysed using Stata 12.0 software. The quantitative data were expressed as mean ± standard deviation (SD) and compared using *t* test. The qualitative data were compared using χ^2 test and Fisher exact test. Univariate and multivariable logistic regression analyses were used to investigate the relationship amongst factors. A probability lower than 0.05 ($P < 0.05$) was considered statistically significant.

Results

Patients' Demographics and Clinical Characteristics

In total, 50 patients (44 men and 6 women, mean age 85.0 ± 3.9 years, range 80-94 years) were included in

this study. The clinical characteristics and the types of infections are shown in Table 1.

A microbiologically documented diagnosis was made in 31 patients (62.0%). The most commonly isolated pathogen was *S. aureus* (38.7%, all were MRSA), followed by *S. haemolyticus* (19.4%, of which 66.7% were methicillin-resistant *S. haemolyticus*), *S. epidermidis* (12.9%, of which 75% were MRSE), *Enterococcus faecium* (12.9%), *Enterococcus faecalis* (9.7%), *S. capitis* (9.7%), *S. cohnii* (6.5%), *S. sciuri* (6.5%), *Enterococcus avium* (3.2%), and *S. hominis* (3.2%).

Most elderly critically ill patients had mixed infections, so most of the patients in the study received a combination of antibiotics. During the vancomycin treatment courses, the antibiotics combined for more than 5 days are shown in Table 1. No patients were treated with amphotericin B or aminoglycosides.

Table 1. Patients Demographics and Clinical Characteristics (n = 50)[a]

Clinical Condition	
Male	44 (88.0)
Age (y)	85.0 ±3.9
Serum creatinine (μmol/L)	73.2 ± 32.4
Creatinine clearance rate (mL/min)	56.5 ± 25.0
Co-morbidities	
Hypertension	36 (72.0)
Ischemic heart disease	21 (42.0)
Diabetes mellitus	17 (34.0)
APACHE II score	23.0 ± 5.1

[a] Data are presented as No. (%) or mean ± standard deviation.

Clinical and Microbiological Outcomes

The clinical efficacy was 74.0% (37/50) in the patients in our study. The 28-day mortality rate was 26.0% (13/50). The clinical efficacy was 77.8% (21/27) in patients with pulmonary infection, 80.0% (8/10) in patients with bloodstream infection, 75.0% (6/8) in patients with pulmonary infection combined with bloodstream infection, 50.0% (1/2) in patients with intra-abdominal infection, 50.0% (1/2) in patients with pulmonary and urinary tract infections, and 0% (0/1) in patients with biliary tract infection. The success group had a lower APACHE II score (21.9 ± 4.6) than the failure group (26.2 ± 5.3; $P = 0.008$). The vancomycin trough concentration was 13.5 ± 2.8 and 15.2 ± 4.5 μg/mL in the success and failure groups, respectively, which were not significantly different ($P = 0.124$). The microbiological success rate was 93.5% (29/31).

Nephrotoxicity During Vancomycin Therapy

Scr and Ccr were routinely monitored in all 50 patients receiving vancomycin. A total of 12 cases (24%) had nephrotoxicity. According to AKIN criteria, 2 cases (4%) with stage 1, 3cases (6%) with stage 2, and 7 cases (14%) with stage 3. Of these, 1 case with stage 1 recovered after drug withdrawal, 2 cases (1case with stage 2 and 1case with stage 3) accepted haemodialysis treatment, and 9 cases died due to secondary multiple organ failure. The information on patients with or without nephrotoxicity is presented in Table 2. APACHE II scores and

Table 2. Comparison of Patients With and Without Nephrotoxicity

Clinical Data	Nephrotoxicity (n=12)	No Nephrotoxicity (n=38)	95% CI	t/χ^2 Value	*P* Value
Age (y)	85.6 ± 4.6	84.8 ± 3.7	-1.808 –3.396	0.613	0.543
APACHE II score	26.9 ± 5.0	21.7 ± 4.6	2.071–8.288	3.35	0.002
Scr (μmol/L)	83.7 ± 42.5	69.9 ± 28.4	-7.590– 35.239	1.298	0.200
Ccr (ml/min)	45.9 ± 20.6	59.9 ± 25.6	-30.246– 2.399	-1.715	0.093
C trough (μg/mL)	16.4 ± 4.5	13.1 ± 2.5	1.259 –5.341	3.252	0.002
Course of treatment (days)	9.9 ± 4.6	21.0 ± 8.9	-16.524 – -5.696	-4.126	0.000
Concomitant nephrotoxic agents					
ACEIs/ARBs	2	5	-	0.000	1.0
COX-2 inhibitors	0	0	-	-	-
NASIDs	0	3	-	-	-
Vasopressor agents	6	8	-	3.791	0.052
Large doses[a]	6	0	-	-	-
Small doses[b]	0	8	-	-	-
Furosemide	12	32	-	3.544	0.198
Daily dose (mg/d)					
>120	5	6	-	-	-
81–120	3	2	-	-	-
41–80	2	8	-	-	-
≤ 40	2	16	-	-	-

Note: Nephrotoxicity, Patients with nephrotoxicity; No nephrotoxicity, Patients without nephrotoxicity; t/χ^2 value, t value for quantitative data, χ^2 value for qualitative data; APACHE II score, APACHE II score before treatment; Scr, serum creatinine before treatment; Ccr, creatinine clearance rate before treatment; C trough, vancomycin trough concentration; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; COX: cyclooxygenase; NASID's: non-steroidal anti-inflammatory drugs; Vasopressor agents, combined use of vasopressor drug;

[a] Large doses of vasopressor drug, norepinephrine ≥0.5 μg/(kg·min) or dopamine ≥20 μg/(kg·min).

[b] Small doses of vasopressor drug, norepinephrine <0.5 μg/(kg·min) or dopamine <20 μg/(kg·min); Furosemide, combined use of furosemide

vancomycin trough concentrations in patients with nephrotoxicity were significantly higher (P = 0.002 and 0.002, respectively) than in those without nephrotoxicity.

Risk Factors of Nephrotoxicity During Vancomycin Therapy

The univariate logistic regression analysis revealed that APACHE II scores before therapy (P = 0.005, odds ratio [OR] = 1.247), vancomycin trough concentrations (P = 0.012, OR = 1.383), course of treatment (P = 0.003, OR = 0.79), and use of diuretics (furosemide with a daily dose of ≤40, 41–80, 81–120, and >120 mg/d) (P = 0.007, OR = 2.124) were associated with nephrotoxicity during vancomycin therapy in elderly patients (Table 3). During the treatment, once the nephrotoxicity occurred, we immediately terminated the use of vancomycin. There should be other risk factors of vancomycin associated nephrotoxicity besides duration of vancomycin exposure. So, we have APACHE II score, trough concentration and use of furosemide in the multivariate analysis.

The risk factors associated with nephrotoxicity in the multivariate analysis demonstrated that APACHE II scores ≥25 (P = 0.002, OR = 35.014), vancomycin trough concentrations ≥15 μg/mL (P = 0.043, OR = 8.292), and the combined use of diuretics (furosemide ≥ 40 mg/d; P = 0.012, OR = 18.708) could increase the risk of nephrotoxicity in elderly patients (Table 4).

Clinical Efficacy, Nephrotoxicity and 28-Day Mortality

To observe whether targeting higher blood concentrations leads to increased efficacy of vancomycin and the risk of nephrotoxicity, we divided the patients into 4 groups with trough concentrations of <10, 10–15, 15–20 and ≥20 μg/mL, and compared the clinical efficacy, 28-day mortality, and nephrotoxicity. Increased trough concentrations of vancomycin were associated with increased nephrotoxicity (0, 20.0%, 25% and 100%, respectively) (Figure 1). Respectively, clinical efficacy was 60%, 86.7%, 58.3%, and 33.3%; the 28-day mortality rate was 20%, 23.3%, 33.3%, and 33.3%; and the trough concentrations were ≤10 μg/mL, 10–15 μg/mL, 15–20 μg/mL, and ≥ 20 μg/mL (Figure 2).

Table 3. Univariate Logistic Regression Analysis of Risk Factors Leading to Nephrotoxicity in Elderly Patients on Vancomycin Therapy

Factors	OR	95% CI	$P > \|z\|$
Age (y)	1.054	0.892–1.246	0.534
APACHE II score	1.247	1.067–1.457	0.005
Scr (μmol/L)	1.013	0.993–1.032	0.203
Ccr (mL/min)	0.973	0.941–1.005	0.098
C trough (μg/mL)	1.383	1.074–1.781	0.012
Course of treatment (days)	0.79	0.67–0.92	0.003
Concomitant nephrotoxic agents			
ACEIs/ARBs	1.32	0.221–7.874	0.761
COX-2 inhibitors	- - -	- - -	- - -
NASIDs	- - -	- - -	- - -
Vasopressor agents	3.75	0.949–14.821	0.059
Large doses[a]	- - -	- - -	- - -
Small doses[b]	- - -	- - -	- - -
Furosemide	2.124	1.224–3.687	0.007

Note: OR, odds ratio; - - -, Data cannot be calculated.
[a] Large doses of vasopressor drug, norepinephrine ≥0.5 μg/(kg·min) or dopamine ≥20 μg/(kg·min.
[b] Small doses of vasopressor drug, norepinephrine <0.5 μg/(kg·min) or dopamine <20 μg/(kg·min).

Table 4. Multivariate Analysis of Risk Factors Leading to Nephrotoxicity in Elderly Patients on Vancomycin Therapy

Factors	OR	95% CI	$P > \|z\|$
APACHE II score before treatment (≥25 points)	35.014	3.838–319.389	0.002
Vancomycin trough concentration (≥15 μg/mL)	8.292	1.072–64.128	0.043
Use of fuosemide (≥40 mg/d)	18.708	1.885–185.662	0.012

OR, odds ratio.

MIC of Bacteria

Our results suggested that when the vancomycin trough concentrations were between 10 and 15 μg/mL, the clinical efficacy was higher. We speculate that this result may be related to the minimum inhibitory concentration (MIC) of bacteria. Because the bacteria were not preserved permanently in our hospital, we only obtained the strains after 2012 (a total of 14 strains). We found that the MIC of most bacteria was ≤1.0 μg/mL (12/14), which generally achieved bacterial eradication.

Discussion

Gram-positive bacteria, particularly multidrug-resistant *S. aureus*, have become the most common cause of nosocomial and community-acquired infections. In the United States, the rate of MRSA infection has increased to 50%-60% according to data from the

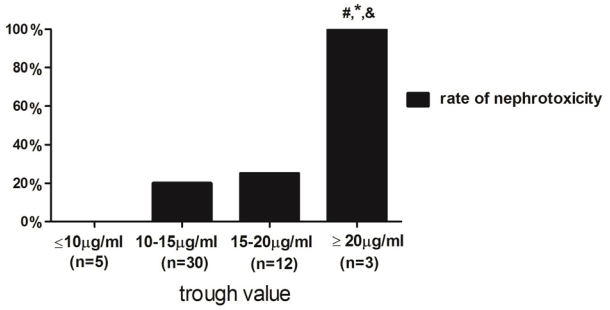

Figure 1. Rate of Nephrotoxicity for the Troughs <10, 10–15, 15–20 and ≥20 μg/mL.
Nephrotoxicity for the troughs ≥ 20μg/mL compared to the troughs <10 μg/mL, P = 0.018; * Nephrotoxicity for the troughs ≥ 20 μg/mL compared to the troughs 10–15 μg/mL, P = 0.015; & Nephrotoxicity for the troughs ≥ 20μg/mL compared to the troughs 15–20 μg/mL, P = 0.044.

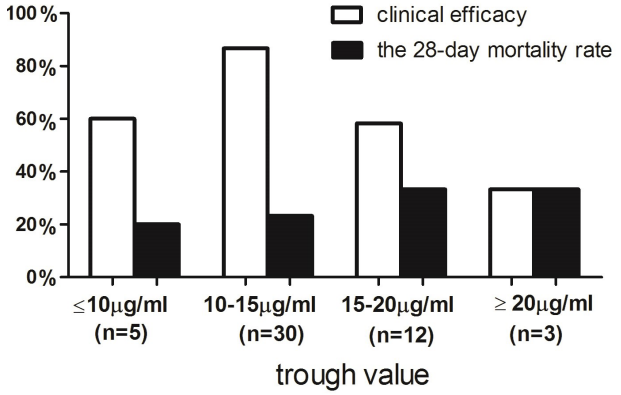

Figure 2. Clinical Efficacy and the 28-Day Mortality Rate for the Troughs <10, 10–15, 15–20 and ≥20 μg/mL. Clinical efficacy and the 28-day mortality rate were not significantly different for the troughs <10, 10–15, 15–20 and ≥ 20 μg/mL.

National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention.[20,21] Similarly, in 2006, bacterial resistance monitoring in 9 major hospitals in China showed that MRSA accounted for 58.4% of infections by *S. Aureus*.[22] Consistent with previous data, in this study, we found that Staphylococci including MRSA and methicillin-resistant *Staphylococcus haemolyticus* were the major gram-positive bacteria isolated in our elderly patients.

Resistant gram-positive bacterial infections including MRSA can result in higher mortality, longer hospital stays, and increased hospital costs.[23] The prompt administration of appropriate antimicrobials is essential for improving clinical outcomes and reducing morbidity and mortality in critical patients with life-threatening infections.[24,25] There are many reports about the effectiveness and safety of vancomycin, which is widely used in clinical practice.[26-28] However, there are limited studies in elderly critically ill patients, particularly those aged ≥80 years. In this study, the clinical efficacy rate reached 74.0%, and the microbiological success rate was 93.5%. The clinical efficacy rate was lower than that of 90% in ICU patients by Dubin et al.[29] This is not surprising, because the immune systems of elderly patients are often affected by ageing, underlying diseases, and medical interventions.[15] Consequently, the efficacy in the elderly is lower than that in adults.

In addition, our data showed that clinical outcomes did not differ significantly between any of those 4 groups. Hermsen et al[30] reported that the clinical outcomes of vancomycin did not differ significantly between high (≥15 μg/mL) and low (<15 μg/mL) trough groups for deep-sited MRSA infections. In thermal injury patients with burns <20% TBSA (total body surface area), no relationship was demonstrated in outcomes with vancomycin therapy for three vancomycin trough strata (<5, 5 to 10, and >10 μg/mL).[31] Therefore, vancomycin trough elevation may not guarantee treatment success,[9] and there may be no real benefit from higher vancomycin trough concentrations (≥15 μg/mL) in elderly critically ill patients. However, a study in critically ill patients with MRSA infections indicated that the trough concentration was higher amongst responders than amongst non-responders (11.64 ± 1.50 μg/mL and 9.25 ± 1.59 μg/mL, respectively; $P = 0.036$).[32] Shankar Lanke, et al. found that the targeted adolescent trough concentration range (for an MIC ≤1 μg/mL) should be lower than that of adults. Specifically, a range of 10–12.5 μg/mL provided the highest likelihood of achieving therapeutic benefit while minimizing the risk of adverse events.[33] Thus, the thresholds and suggested dosing regimens differ in different populations, particularly within elderly patients.

The incidence of nephrotoxicity caused by vancomycin ranges from 2%–28%.[5] The nephrotoxicity caused by vancomycin therapy was 24% in this study. This is relatively higher in comparison to our results, most likely because the subjects in our study were elderly critically ill patients, who were associated with a variety of underlying diseases accompanied by single or multiple organ dysfunctions.[34] In our study, APACHE II scores were higher in the patients with nephrotoxicity. The logistic regression analysis showed that APACHE II scores ≥25 points could be independent risk factors leading to nephrotoxicity. The APACHE II score reflects the severity of the acute illnesses in patients,[17] so it suggests that those patients with greater illness severity are at a higher risk of nephrotoxicity when being treated with vancomycin.[34] Elting et al[35] investigated nephrotoxicity during vancomycin treatment in 726 patients with cancer, aged 17 to 86 years, and found that the incidence of nephrotoxicity was higher in patients with an APACHE II score ≥40 points than in those with an APACHE II score <40 points.

According to the 2009 recommendations of the Infectious Diseases Society of America, vancomycin trough concentrations in the blood should generally be maintained at 10 μg/mL or higher, and 15-20 μg/mL for severe infections.[8] However, the guidelines also note that evidence regarding safety when the trough concentration is maintained at 15–20 μg/mL, is limited and warrants further studies. In this study, we routinely monitored vancomycin trough concentrations in elderly patients with severe infections and adjusted vancomycin dosage based on the results. The results revealed that vancomycin trough concentration was 16.4 ± 4.5 μg/mL in the patients with nephrotoxicity, which was significantly higher than the concentration of 13.1 ± 2.5 μg/mL in those without nephrotoxicity. The multivariate logistic regression analysis showed that a trough concentration ≥15 μg/

mL may be an independent risk factor of nephrotoxicity during vancomycin treatment. Lodise et al[12] explored the relationship between vancomycin concentrations and nephrotoxicity from the pharmacokinetic point of view and reported that the incidence of nephrotoxicity was 33% and 21% for vancomycin concentrations of >20 and 10-20 μg/mL, respectively, but it was reduced to 5% when vancomycin concentration was <10 μg/mL. Another study[11] demonstrated that the incidence of nephrotoxicity can be very high, even up to 65%, when the vancomycin concentration exceeds the recommended range of >20 μg/mL. Thus, the trough concentration was closely related to nephrotoxicity during vancomycin treatment.

Based on multivariate regression analyses, some researchers[36] found that the use of loop diuretics is positively correlated with the incidence of nephrotoxicity caused by vancomycin in elderly patients. Our multivariate regression analysis also showed that furosemide use (daily dose ≥40 mg/d) was an independent risk factor leading to nephrotoxicity. Diuretics can decrease the fluid load in patients, either directly (decrease the blood supply to the kidneys) or indirectly (decrease the extracellular fluid), resulting in renal haemodynamic abnormalities, greatly reduced renal blood perfusion, lowering glomerular filtration rate (GFR), and prerenal azotemia or acute tubular necrosis.[37,38]

Our study has several important limitations. First, it was a retrospective non-experimental study, and all information was collected based on medical records; therefore, causality cannot be determined. Second, clinical efficacy was evaluated in a small sample of patients with different types of infections and microbes, and also most patients received a combination of antibiotics; therefore, clinical effects could not be attributed to vancomycin alone. Third, critically ill patients suffering from different infections may develop rapid renal failure because of intoxication together with other factors such as low reserve, diabetes, hypertension, etc. Thus, high vancomycin concentrations may be the cause, effect, or both, of nephrotoxicity. Lastly, our results may not be applicable to other centres because our study was performed in a single institution.

In conclusion, elderly critically ill patients have a relatively high risk of nephrotoxicity during vancomycin therapy. We did not find that higher vancomycin trough concentrations could lead to better clinical outcomes in very old critically ill patients. Trough concentrations ≥15 μg/mL, furosemide use (daily dose ≥40 mg/d), and APACHE II scores ≥25 points maybe independent risk factors leading to nephrotoxicity in elderly patients undergoing vancomycin therapy.

Authors' Contribution

MH contributed to the data collection, data analysis and writing of the manuscript. HW contributed to the data collection. JZ contributed to the data analyses. SZ and MX contributed to the project design, data analysis, and writing of the manuscript. SZ is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

Ethical approval was given by the medical ethics committee of the First Affiliated Hospital of Nanjing Medical University with the following reference number: 2014-SR-049.

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