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

Min Huang, PhD, MD; Hao Wu, PhD, MD; Jing Zhou, PhD, MD; Min Xu, MD; Suming Zhou, PhD, MD

1Department of Geriatrics, The First Affiliated Hospital of Nanjing Medical University, Nanjing, 210029, P. R. China
2Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, 210029, P. R. China
3Department of Hematology, Zhangjiagang First People’s Hospital, Suzhou, 215600, P. R. China

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


Received: January 7, 2018, Accepted: May 25, 2018, ePublished: August 1, 2018

Introduction

Vancomycin is widely used for infections caused by methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant Staphylococcus epidermidis (MRSE), and Enterococcus. 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. Specifically, elderly patients who suffer from severe infections, receive more antibiotics due to their compromised immune function and underlying diseases. Although new antibacterial drugs such as linezolid, daptoimycin, telavancin and cephalosporins have been applied for the clinical treatment of MRSA infections, 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. However, vancomycin has a narrow therapeutic range and can cause several adverse effects including fever, chills, phlebitis, allergic reactions, nephrotoxicity, and neutropenia. 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.

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%. Recently, Hanrahan et al 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. Because vancomycin is eliminated from the body mainly via the kidneys, reduced renal clearance leads to increased vancomycin trough
concentrations, which may result in nephrotoxicity.\textsuperscript{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 furosemide) 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 \( \geq 80 \) 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;\textsuperscript{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 \( \times \) Ccr/d (mg).\textsuperscript{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.\textsuperscript{8} The target concentrations were 10-15\( \mu \)g/mL in bloodstream infections and 15-20\( \mu \)g/mL in other types of infections.\textsuperscript{10,13} 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 (\( \mu \)mol/L) \( \times \) 24 h urine volume (ml)/(1440 \( \times \) Scr (\( \mu \)mol/L)).\textsuperscript{19}

Evaluation of Nephrotoxicity
The occurrence of nephrotoxicity was defined as an increase in Scr levels of 44.2 \( \mu \)mol/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.\textsuperscript{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 \( \pm \) standard deviation (SD) and compared using \( t \) test. The qualitative data were compared using \( \chi^2 \) 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 \( \pm \) 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. colinii* (6.5%), *S. sciuri* (6.5%), *Enterococcus avium* (3.2%), and *S. hominitis* (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)

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Male (n=44)</th>
<th>Age (y)</th>
<th>Serum creatinine (μmol/L)</th>
<th>Creatinine clearance rate (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>36 (72.0)</td>
<td>85.0 ± 3.9</td>
<td>73.2 ± 32.4</td>
<td>56.5 ± 25.0</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>21 (42.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (34.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>23.0 ± 5.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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, 3 cases (6%) with stage 2, and 7 cases (14%) with stage 3. Of these, 1 case with stage 1 recovered after drug withdrawal, 2 cases (1 case with stage 2 and 1 case 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 creatinine clearance rates for patients with and without nephrotoxicity are shown in Table 2.

### Table 2. Comparison of Patients With and Without Nephrotoxicity

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>Nephrotoxicity (n=12)</th>
<th>No Nephrotoxicity (n=38)</th>
<th>95% CI</th>
<th>t/χ² Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>85.6 ± 4.6</td>
<td>84.8 ± 3.7</td>
<td>-1.808 – 3.396</td>
<td>0.613</td>
<td>0.543</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>26.9 ± 5.0</td>
<td>21.7 ± 4.6</td>
<td>2.071 – 8.288</td>
<td>3.35</td>
<td>0.002</td>
</tr>
<tr>
<td>Scr (μmol/L)</td>
<td>83.7 ± 45.2</td>
<td>69.9 ± 28.4</td>
<td>-7.590 – 35.239</td>
<td>1.298</td>
<td>0.200</td>
</tr>
<tr>
<td>Ccr (ml/min)</td>
<td>45.9 ± 20.6</td>
<td>59.9 ± 25.6</td>
<td>-10.246 – 2.399</td>
<td>-1.715</td>
<td>0.093</td>
</tr>
<tr>
<td>C trough (μg/mL)</td>
<td>16.4 ± 4.5</td>
<td>13.1 ± 2.5</td>
<td>1.259 – 5.341</td>
<td>3.252</td>
<td>0.002</td>
</tr>
<tr>
<td>Course of treatment (days)</td>
<td>9.9 ± 4.6</td>
<td>21.0 ± 8.9</td>
<td>-16.524 – 5.696</td>
<td>-4.126</td>
<td>0.000</td>
</tr>
<tr>
<td>Coexistent nephrotoxic agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEIs/ARBs</td>
<td>2</td>
<td>5</td>
<td>-</td>
<td>-0.000</td>
<td>1.0</td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vasopressor agents</td>
<td>6</td>
<td>8</td>
<td>-</td>
<td>3.791</td>
<td>0.052</td>
</tr>
<tr>
<td>Large doses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Small doses&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Furosemide</td>
<td>12</td>
<td>32</td>
<td>-</td>
<td>3.544</td>
<td>0.198</td>
</tr>
<tr>
<td>Daily dose (mg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;120</td>
<td>5</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>81–120</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>41–80</td>
<td>2</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≤ 40</td>
<td>2</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Nephrotoxicity, Patients with nephrotoxicity; No nephrotoxicity, Patients without nephrotoxicity; t/χ² value, t value for quantitative data, χ² 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; NSAID’s: non-steroidal anti-inflammatory drugs; Vasopressor agents, combined use of vasopressor drug;

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

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

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         | $P > | \chi^2 |$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score before treatment ≥25</td>
<td>35.014</td>
<td>3.838–319.389</td>
<td>0.002</td>
</tr>
<tr>
<td>Vancomycin trough concentration ≥15 μg/mL</td>
<td>8.292</td>
<td>1.072–64.128</td>
<td>0.043</td>
</tr>
<tr>
<td>Use of furosemide ≥40 mg/d</td>
<td>18.708</td>
<td>1.885–185.662</td>
<td>0.012</td>
</tr>
</tbody>
</table>

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...
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. 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, so it suggests that those patients with greater illness severity are at a higher risk of nephrotoxicity when being treated with vancomycin. Elting et al 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. 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 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 study13 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 researchers46 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.

Funding
This work was supported by the project of critical care medicine of the key clinical specialty of Jiangsu province.

References
12. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time
Efficacy of Vancomycin on Gram-Positive Bacterial Infection in Elderly Critical Patients


