Assessment of acute kidney injury in neurologically and traumatically injured intensive care patients receiving large vancomycin doses

Casey C. May, Beth L. Erwin\textsuperscript{1}, Margaret Childress\textsuperscript{1}, Josh Cortopassi\textsuperscript{1}, Garrett Curtis\textsuperscript{1}, Tyson Kilpatrick\textsuperscript{1}, Jennifer Taylor\textsuperscript{1}, Bonnie Vance\textsuperscript{1}, Doug Wylie\textsuperscript{1}

**ABSTRACT**

**Background:** Previous reports note that in a mixed patient population, vancomycin doses $>4$ g/day are associated with increased rates of acute kidney injury (AKI).

**Objective:** The objective of the study is to determine if vancomycin regimens $>4$ g/day are associated with a higher incidence of AKI in neurocritical care unit (NCCU) and trauma/burn Intensive Care Unit (TBICU) patients.

**Materials and Methods:** This single-centered, retrospective study enrolled adult patients initiated on vancomycin in the NCCU and TBICU at an academic medical center during 2016. Based on maximum steady-state dose exposure, patients were separated into two groups: $\leq 4$ g/day and $>4$ g/day. The primary outcome of incidence of AKI was defined by the AKI Network criteria.

**Results:** A total of 284 patients were screened for eligibility; 165 patients met inclusion criteria, 98 patients received $\leq 4$ g/day and 67 patients received $>4$ g/day. The $>4$ g/day group had a lower mean age ($32.6 \pm 11.1$ vs. $47.8 \pm 16.2$, $P < 0.001$), included more male patients (81% vs. 60%, $P = 0.008$), were more often treated for a central nervous system infection (31% vs. 11%, $P = 0.001$), had, on average, more concomitant use of nephrotoxic drugs ($2.2 \pm 1.2$ vs. $1.8 \pm 0.9$, $P = 0.02$) and had a higher exposure to contrast (94% vs. 79%, $P < 0.001$). The primary outcome of AKI occurred in 14 patients receiving $\leq 4$ g/day and five patients receiving $>4$ g/day which was not statistically significant (14% vs. 7%, $P = 0.22$).

**Conclusions:** Our results indicate that administering $>4$ g/day of vancomycin to achieve therapeutic vancomycin troughs does not appear to lead to an increased incidence of AKI in a mixed NCCU and TBICU population.

**Key Words:** Neurology, pharmacodynamics, pharmacokinetics, trauma, vancomycin

**INTRODUCTION**

Augmented renal clearance (ARC), or enhanced renal function, is generally not considered or well recognized by intensive care clinicians. ARC was first identified in 1978 and is thought to be due to increased levels of acute phase proteins, alterations in vascular tone, cardiac output, and major organ blood flow, resulting in a hyperdynamic state.\textsuperscript{[1,2]} Defined by a creatinine clearance (CrCl) $>130$ ml/min/1.73 m$^2$, ARC has been...
described in various critically ill populations including sepsis, febrile neutropenia, burn, polytrauma, traumatic brain injury, hemorrhagic stroke, and aneurysmal subarachnoid hemorrhage.\[5-9\]

ARC was initially identified when subtherapeutic levels of medications, such as vancomycin and aminoglycosides, were consistently obtained. Various descriptions of this phenomenon have been documented and suggest that vancomycin elimination is enhanced, necessitating an intensified dosing regimen to achieve therapeutic serum concentrations.\[6,10-13\] To date, there has been no documentation of rates of acute kidney injury (AKI) with increased vancomycin doses in patients with ARC.\[10,11,14\]

Vancomycin is the antibiotic of choice for empiric and targeted therapy for various Gram-positive infections.\[15-17\] A serum vancomycin trough of 15–20 µg/mL is the recommended target for serious infections including bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe skin and soft-tissue infections.\[15,18\] Due to the narrow therapeutic range, dosing vancomycin remains challenging in all patients; however, it becomes even more difficult when dosing critically ill patients exhibiting ARC with one report noting doses reaching 50–60 mg/kg/day to achieve goal troughs.\[19\]

In 2008, a single center, retrospective study completed in a mixed patient population initiated on vancomycin identified a correlation between vancomycin doses ≥4 g/day and a higher likelihood of vancomycin-related nephrotoxicity.\[20\] Our experience indicates patients in the neurocritical care unit (NCCU) and trauma/burn Intensive Care Unit (TBICU) often require >4 g/day to achieve therapeutic levels.

The purpose of this study was to determine if vancomycin regimens exceeding 4 g/day in a mixed NCCU and TBICU population led to a higher incidence of AKI. The hypothesis was that this neurologically and/or traumatically injured critically ill-patient population would not have a higher incidence of AKI when receiving >4 g/day of vancomycin as compared to those on a lower daily dose of ≤4 g/day.

**MATERIALS AND METHODS**

This was a single-center, retrospective study that included adult patients admitted to the NCCU and TBICU at an academic medical center in 2016. This study was approved by the Institutional Review Board with a waiver of informed consent. Patients were divided into two groups: patients who received a maximum daily dose of ≤4 g/day of vancomycin and those who received >4 g/day of vancomycin. Patients were enrolled if they were ≥18 years old, had received vancomycin and had one steady-state vancomycin concentration of at least 10 µg/mL. Patients were excluded if they were pregnant, incarcerated, had renal dysfunction at the time of vancomycin initiation (end-stage renal disease requiring dialysis or serum creatinine (SCr) >2.0 mg/dL), neutropenia (absolute neutrophil count of <1000 cells/mm³), cystic fibrosis, or if they received vancomycin at an outside hospital before transfer.

Clinical pharmacists are consulted to initiate and manage vancomycin for all inpatients based on institutional dosing guidelines and patient-specific pharmacokinetics. Per these guidelines, all patients received intermittently dosed vancomycin no more frequently than every 6 h (continuous infusions were not used), and the goal steady-state serum vancomycin trough concentration was 10–20 µg/mL for empiric treatment and 15–20 µg/mL for serious infections as defined above.

Medical records were retrospectively reviewed, and standardized data collection forms were utilized for obtaining all data. The following baseline characteristics were collected: age, gender, weight, Glasgow Coma Scale score, Acute Physiology and Chronic Health Evaluation II score, SCr, hospital and ICU admission date and time, and presence of previous health-care exposure. Data collected for characterizing the vancomycin regimen included the date and time of initiation, dose, and all steady-state, therapeutic trough concentrations. Steady-state levels were defined as the trough level before the fourth or later maintenance dose. The indication for vancomycin therapy and all positive cultures were documented. Daily SCr was collected starting 5 days before vancomycin initiation until 72 h after therapy completion. The estimated CrCl (CrClₑ) was calculated using the Cockcroft-Gault formula standardized to body surface area (BSA) using actual body weight. This formula was demonstrated by Hoste et al., to most closely correlate with actual CrCl (CrClₐ) in a critically ill population.\[21\] This formula is defined below:

\[
CrClₑ = \frac{(140 - \text{Age}) \times \text{Wt} \times 1.73}{S\text{cr} \times 72 \times \text{BSA}} \times 0.85 \text{ if female}
\]

Receipt of the following nephrotoxic drugs was noted if the patient received the drug at any point during the 10 days before the start of vancomycin until 72 h after completion of therapy: aminoglycosides, amphotericin, cyclosporine, tacrolimus, piperacillin–tazobactam, cefepime, nafcillin, loop diuretics, nonsteroidal anti-inflammatory drug (excluding aspirin), acyclovir, mannitol, and sulfamethoxazole-trimethoprim. Co-administration of vasopressors was documented if given anytime during vancomycin treatment, and it was noted if intravenous (IV) contrast was administered at any point during the 7 days before vancomycin initiation until 72 h after completion.
The primary outcome was the incidence of AKI as defined by the AKI Network (AKIN) criteria.[22] If SCr increased by ≥0.3 mg/dL or by ≥150% from baseline on two consecutive days (up to 72 h after completion of therapy), the patient was noted to have AKI. The SCr on vancomycin day one was considered the patient’s baseline when evaluating the primary outcome. The secondary outcome was the proportion of patients who exhibited ARC (CrCl >130 ml/min/1.73 m²) based on their CrCl on the day vancomycin therapy was initiated.

Basic descriptive analyses including mean, standard deviation, and percentages were used to summarize baseline characteristics and results. Normally distributed data were assessed using the Student’s t-test for continuous data and the Chi-squared test or Fisher’s exact test for categorical data where appropriate.

RESULTS

A total of 284 patients were admitted to the NCCU or TBICU and initiated on vancomycin therapy in 2016, of which 165 met inclusion criteria. Of these, 98 patients received ≤4 g/day and 67 patients received >4 g/day [Figure 1].

Baseline characteristics are displayed in Table 1, demonstrating that the ≤4 g/day group had a higher mean age (47.8±16.2 vs. 32.6±11.1, P<0.001) and included fewer male patients (60% vs. 81%, P = 0.008) compared to the >4 g/day group. Patients in the ≤4 g/day group were less likely to be treated for a central nervous system (CNS) infection (11% vs. 31%, P = 0.001).

On average, each patient in the ≤4 g/day group and >4 g/day group, respectively, received 1.8±0.9 and 2.2±1.2 (P = 0.02) concomitant nephrotoxic drugs [Table 1]. Patients in the ≤4 g/day group did not receive contrast as often as those in the >4 g/day group (77 [79%] vs. 63 [94%], P<0.001) and significantly more patients in the ≤4 g/day group were exposed to vasopressors (32 [33%] vs. 12 [18%], P = 0.04).

Table 2 highlights the vancomycin dose, duration, and trough levels. The dose of vancomycin was significantly lower in the ≤4 g/day group at 2,921±758 mg/day as compared to 5,220±586 mg/day in the >4 g/day group at (P<0.001).

Figure 1: Summary of study patient selection. *Other includes pregnant patients, patients admitted to the pulmonary service, and prisoners

Figure 2: Primary and secondary outcomes. (a) Incidence of acute kidney injury. *P value determined by Fisher’s exact test. (b) Proportion of patients who exhibited augmented renal clearance on the day of vancomycin initiation. †P value determined by Chi-squared test
The primary outcome of AKI occurred in 14 patients receiving ≤4 g/day and 5 patients receiving >4 g/day which did not meet statistical significance [14% vs. 7%, $P = 0.22$, Figure 2a]. For the secondary outcome, 41% in the ≤4 g/day group versus 80% of patients in the >4 g/day group met criteria for ARC [$P < 0.001$, Figure 2b].

**DISCUSSION**

This is the first study, to the best of our knowledge, to evaluate the incidence of AKI associated with vancomycin doses >4 g/day in patients admitted to an NCCU or TBICU. Our results indicate that administering >4 g/day of vancomycin to achieve therapeutic troughs does not
increase the incidence of AKI in a mixed NCCU and TBICU population when compared to those who received a lower dose (≤4 g/day). In addition, 80% of the patients receiving >4 g/day of vancomycin met criteria for having ARC. It is important to note that the overall incidence of AKI in the >4 g/day group was low; however, we believe this is a true representation of this patient population due to the nature of their injury, younger age, and presence of ARC.

The definition of vancomycin-induced nephrotoxicity is varied and inconsistent. Several publications, define vancomycin nephrotoxicity by a 0.5 mg/dL elevation in SCr if initial SCr is ≤3 mg/dL or a 50% increase from baseline, whichever is greater.[18,23] Our group agreed that the AKIN criteria were more applicable in our population as compared to the generic SCr increase of 0.5 mg/dL from baseline and are more sensitive requiring a lower SCr increase to meet the outcome of having AKI. The AKIN criteria have also been utilized in a more recent study evaluating vancomycin-induced AKI in the critically ill, identifying AKI in 19% of patients following 6 days of vancomycin therapy.[24]

Although patients in the >4 g/day group received about two times more vancomycin per day when compared to the ≤4 g/day group, there was no increased risk of AKI. Our study noted that, on average, patients in the >4 g/day group required 58.6±17 mg/kg/day of vancomycin to achieve therapeutic vancomycin troughs. Our group is not the first to describe increased vancomycin dose requirements in this patient population. One study found that hemorrhagic stroke patients often have subtherapeutic troughs with doses ranging from 35 to 50 mg/kg/day. They noted that the pharmacokinetics of vancomycin were statistically different compared to predictions: elimination rate constant measured 0.122/h compared to a predicted value of 0.086/h, half-life measured 6.4 h compared to the predicted value of 8.9 h, and trough concentration measured 10.2 µg/mL compared to a predicted value of 18.3 µg/mL.[6]

Additionally, when treating methicillin-resistant Staphylococcus aureus pneumonia in the critically ill adult trauma patient, one group found that doses exceeding 1g every 8 h were required to meet the prespecified goal trough levels. This group compared 19 patients who received an initial vancomycin dose of 1 g every 12 h to 17 patients who received an initial dose of 1 g every 8 h. An important finding was that only 23.4% of patients in the 1 g every 8 h group reached a trough of >15 µg/mL compared to zero patients in the 1 g every 12 h group, demonstrating that doses exceeding 3 g/day are needed to reach a vancomycin trough level of 15 µg/mL.[23] These published examples, along with our study, demonstrate that traumatically and neurologically critically ill patients routinely require higher daily doses to meet the Infectious Diseases Society of America recommendation of a target vancomycin trough of 15–20 µg/mL for serious infections.[15,18]

It is important to note that in our study we excluded patients who never achieved a vancomycin trough of 10 µg/mL because we believed that including patients that never became therapeutic on vancomycin would be a major confounder. We did, however, included all supratherapeutic levels in our assessment to assess for possible harm of the larger vancomycin doses. Vancomycin steady state was determined by obtaining a trough level before the fourth or later maintenance dose. We acknowledge that renal function was likely variable during the interval between the first dose of vancomycin and measured trough and that steady state was potentially variable in a concordant fashion. However, it is unlikely that this impacted the validity of the steady-state assumption since the measurement parameter was applied consistently across all measured values.

As mentioned above, we found a significant difference between our mean trough levels (13.6µg/mL in the ≤4 g/day group and 14.9 µg/mL in the >4 g/day group, P = 0.008). Although statistically significant, we believe there is no clinical significance between these two levels. If there was a clinical difference in mean vancomycin trough levels, we would have expected the >4 g/day to have higher rates of vancomycin-induced AKI as there have been reports of increased nephrotoxicity with higher vancomycin troughs. A prospective multicenter trial published in 2011 found an increased odds ratio of vancomycin-induced nephrotoxicity in patients who had mean vancomycin trough concentrations ≥15 µg/mL compared to those who had mean trough concentrations <15 µg/mL (odds ratio 3.643; 95% confidence interval, 1.749–7.587).[24]

Despite differences in demographics and baseline characteristics, we believe these differences contributed to the utilization of higher vancomycin doses and were expected. Differences in age, renal function, and sex are factors associated with ARC that require higher daily doses.[27] The percentage of patients requiring more aggressive dosing for CNS infections was lower in the ≤4 g/day group than the >4 g/day group (11% vs. 31%, P = 0.001). Although more patients in the >4 g/day group had a documented CNS infection, it is important to note that most patients in each group were being treated for pneumonia; therefore, the higher dose requirement in this population was not isolated to those with CNS infections. Differences in concomitant nephrotoxic drug exposure were detected and the ≤4 g/day group had higher vasopressor exposure. This could have led to a higher rate of AKI in the ≤4 g/day group. It is important to note that many times patients in the NCCU and TBICU received vasopressors to augment their blood
pressure above supraphysiologic numbers to improve profusion. We did not look into the indication or duration of vasopressor utilization; therefore, the true impact of vasopressor exposure cannot be determined.

When evaluating the significance of our findings, it is important to recognize the differences between the patients enrolled in our study compared to those in the only published study linking daily vancomycin dose to AKI. The aforementioned study included all patients who received vancomycin for >48 h, of which, only 18 patients received high dose vancomycin (defined as >4 g/day). In addition, they excluded those who received IV contrast dye in the previous 7 days. As demonstrated in our findings, 79% of patients in the ≤4 g/day group and 94% of patients in the >4 g/day group received IV contrast around the time of their vancomycin therapy. Because of this, previously published results may not be generalizable to mixed NCCU, and TBICU patients as many of these patients received IV contrast to investigate their injuries.

This study has several limitations. First, the retrospective design and determination of vancomycin indication and dosing relied on documentation in the electronic medical record (EMR). EMR documentation was used to assess each vancomycin dose and level for appropriateness with respect to time drawn and goal level. In addition, urine output and fluid status were not assessed, as this information was not readily available in our EMR during the time. We acknowledge the fact that if a patient’s fluid status was not optimized, this too could have led to AKI. Of note, CrCl was calculated based on SCr using the Cockcroft-Gault formula standardized to BSA. Although Hoste et al. demonstrated this formula correlates with CrCl in a critically ill population, it is not the most accurate predictor of renal function; a 24-h urine collection is the gold standard. Finally, a power analysis was not performed because to our knowledge, there is no known rate of vancomycin-induced AKI in an NCCU or TBICU patient population, and due to the small sample size, the possibility of a Type-II error cannot be ruled out.

This retrospective study demonstrates that large vancomycin doses (>4 g/day) are not associated with AKI in the NCCU and TBICU patient population. This study, along with previous studies published in this area, raise very important questions regarding the proper dosing of all renally eliminated drugs in the ARC patient population. Clinicians are identifying that higher doses of monitorable drugs should be utilized in patients with ARC because we are obtaining subtherapeutic levels. We fear that there could be significant under-dosing in this population, which makes dose optimization for drugs that are not monitored using serum drug levels a very important area for future evaluation.

CONCLUSIONS

This is the first study evaluating large vancomycin doses and the incidence of AKI in neurologically and traumatically injured critically ill patients. Based on this study, administering vancomycin doses >4 g/day, in this population of critically ill patients, does not appear to lead to an increased incidence of AKI when compared to administering ≤4 g/day. Moving forward, when dosing vancomycin for these patients, it is important to consider the site of infection, determine the patient’s actual renal function and utilize patient-specific dosing and monitoring to ensure patients are receiving a safe and efficacious dose.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Loirat P, Rohan J, Baillet A, Beaufils F, David R, Chapman A, et al. Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. N Engl J Med 1978;299:915-9.
2. Udy AA, Roberts JA, Lipman J. Implications of augmented renal clearance in critically ill patients. Nat Rev Nephrol 2011;7:539-43.
3. Udy A, Boots R, Senthuran S, Stuart J, Deans R, Lassig-Smith M, et al. Augmented creatinine clearance in traumatic brain injury. Anesth Analg 2010;111:1505-10.
4. Minville V, Aeshnoune K, Ruiz S, Breden A, Georges B, Seguin T, et al. Increased creatinine clearance in polytrauma patients with normal serum creatinine: A retrospective observational study. Crit Care 2011;15:R49.
5. Conil JM, Georges B, Fourcade O, Seguin T, Lavit M, Samii K, et al. Assessment of renal function in clinical practice at the bedside of burn patients. Br J Clin Pharmacol 2007;63:583-94.
6. Morbitzer KA, Jordan JD, Sullivan KA, Durr EA, Olm-Shipman CM, Rhoney DH. Vancomycin pharmacokinetic parameters in patients with hemorrhagic stroke. Neurocrit Care 2016;25:250-7.
7. May CC, Arora S, Parli SE, Fraser JF, Bastin MT, Cook AM. Augmented renal clearance in patients with subarachnoid hemorrhage. Neurocrit Care 2015;23:374-9.
8. Hirai K, Ishii H, Shimoshikiry o T, Shimomura T, Tsuji D, Inoue K, et al. Augmented renal clearance in patients with febrile neutropenia is associated with increased risk for subtherapeutic concentrations of vancomycin. Ther Drug Monit 2016;38:706-10.
9. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function – Measured and estimated glomerular filtration rate. N Engl J Med 2006;354:2473-83.
10. Cook AM, Arora S, Davis J, Pittman T. Augmented renal clearance of vancomycin and levetiracetam in a traumatic brain injury patient. Neurocrit Care 2018;29:210-4.
11. Lonsdale DO, Udy AA, Roberts JA, Lipman J. Antibacterial therapeutic drug monitoring in cerebrospinal fluid: Difficulty in achieving adequate drug concentrations. J Neurosurg1998;299:915-9.
12. Minkuti R, Briedis V, Stepanaviciute R, Vitkauskiené A, Mačiulaitis R. Augmented renal clearance – An evolving risk factor to consider during the treatment with vancomycin. J Clin Pharm Ther 2013;38:462-7.
13. Baptista JP, Sousa E, Martins PJ, Pimentel JM. Augmented renal clearance in septic patients and implications for vancomycin optimisation. Int J Antimicrob Agents 2012;39:420-3.
14. Baptista JP, Roberts JA, Sousa E, Freitas R, Deveza N, Pimentel J. Decreasing the time to achieve therapeutic vancomycin concentrations
in critically ill patients: Developing and testing of a dosing nomogram. Crit Care 2014;18:654.

15. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz R, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:e18-55.

16. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84.

17. Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Michael Scheld W, et al. 2017 infectious diseases society of america’s clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis 2017;64:e34-e65.

18. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, et al. Vancomycin therapeutic guidelines: A summary of consensus recommendations from the infectious diseases society of America, the American Society of health-system pharmacists, and the society of infectious diseases pharmacists. Clin Infect Dis 2009;49:325-7.

19. Albanèse J, Léone M, Bruguerolle B, Ayem ML, Lacarelle B, Martin C, et al. Cerebrospinal fluid penetration and pharmacokinetics of vancomycin administered by continuous infusion to mechanically ventilated patients in an Intensive Care Unit. Antimicrob Agents Chemother 2000;44:1356-8.

20. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother 2008;52:1330-6.

21. Hoste EA, Damen J, Vanholder RC, Lameire NH, Delanghe JR, Van den Hauwe K, et al. Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. Nephrol Dial Transplant 2005;20:747-53.

22. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

23. Bailie GR, Neal D. Vancomycin ototoxicity and nephrotoxicity. A review. Med Toxicol Adverse Drug Exp 1988;3:376-86.

24. Minejima E, Choi J, Beiringer P, Lou M, Tse E, Wong-Beringer A, et al. Applying new diagnostic criteria for acute kidney injury to facilitate early identification of nephrotoxicity in vancomycin-treated patients. Antimicrob Agents Chemother 2011;55:3278-83.

25. Patanwala AE, Norris CJ, Nix DE, Kopp BJ, Erstad BL. Vancomycin dosing for pneumonia in critically ill trauma patients. J Trauma 2009;67:802-4.

26. Bosso JA, Nappi J, Rudisill C, Wellein M, Bookstaver PB, Swindler J, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: A prospective multicenter trial. Antimicrob Agents Chemother 2011;55:5475-9.

27. Barletta JF, Mangram AJ, Byrne JF, Sucher JF, Hollingsworth AK, Ali-Osman FR, et al. Identifying augmented renal clearance in trauma patients: Validation of the augmented renal clearance in trauma intensive care scoring system. J Trauma Acute Care Surg 2017;82:665-71.

28. Lin Wu FL, Liu SS, Yang TY, Win MF, Lin SW, Huang CF, et al. A larger dose of vancomycin is required in adult neurosurgical intensive care unit patients due to augmented clearance. Ther Drug Monit 2015;37:609-18.

29. Campassi ML, Gonzalez MC, Masevicius FD, Vazquez AR, Moseinco M, Navarro NC, et al. Augmented renal clearance in critically ill patients: Incidence, associated factors and effects on vancomycin treatment. Rev Bras Ter Intensiva 2014;26:13-20.

30. Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J. Augmented renal clearance: Implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 2010;49:1-6.