Vancomycin induced acute kidney injury: a review of the literature

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Abstract

Vancomycin has been widely used for its activity against Gram positive bacteria and is often the first choice for methicillin-resistant Staphylococcus aureus (MRSA). The current guidelines recommend trough levels of 15-20 mcg/mL to treat these resistant organisms. Higher trough levels are synonymous with higher doses and in turn predispose patients to adverse events. The most commonly reported adverse event is nephrotoxicity and/ or acute kidney injury. If detected early, this insult is reversible. We review the literature on vancomycin nephrotoxicity in the adult medicine and critical care patients, highlighting risk factors and differences between continuous and intermittent dosing regimens.

Key words: vancomycin, acute kidney injury, continuous infusion

Vancomycin, a bactericidal glycopeptide, was first introduced in 1956 and is one of the most commonly used antibiotics in the US. It inhibits cell wall synthesis of Gram positive bacteria. According to the American Society of Health-System Pharmacists, the Infectious Disease Society of America, and the Society of Infectious Diseases Pharmacists, the current recommended guidelines for vancomycin dosing are 15–20 mg/kg given every 8 to 12 hours for most patients with normal renal function to achieve optimal trough concentrations no less than 10 mcg/mL to avoid the development of resistance.[1,2] The use of higher doses can cause adverse events, such as nephrotoxicity and acute kidney injury, in patients with normal baseline renal function, critically ill patients, and obese patients. There are numerous theories about vancomycin-induced nephrotoxicity, including oxidative stress and allergic interstitial nephritis.[3,4]

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The most frequently used definition of vancomycin associated nephrotoxicity is a 50% increase in serum creatinine over the baseline level or a decrease in creatinine clearance of ≥ 50% from baseline for two consecutive days.[4] Nephrotoxicity can develop within four days to three weeks after the start of therapy, and retrospective studies have shown that it resolves in the majority of cases if it is detected early and vancomycin is discontinued. [5–7,8,9] The incidence of vancomycin associated nephrotoxicity ranges from 5% to 65%.[10] Risk factors for vancomycin induced kidney injury include high dose therapy, prolonged therapy, obesity, concomitant use of other nephrotoxins (such as aminoglycosides), critical illness requiring ICU admission, the use of vasopressors, and high Acute Physiology and Chronic Health Evaluation II scores.[3,11-12]

Continuous infusion dosing regimens are often used to reduce the development of acute kidney injury of nephrotoxicity; however, the current literature provides conflicting results on this strategy. Cataldo and colleagues conducted a systematic review and meta-analysis comparing the effect of continuous

infusions of vancomycin with intermittent infusions in adult patients with Gram positive infections. Their meta-analysis showed that vancomycin continuous infusions were associated with a lower risk of nephrotoxicity when compared with intermittent infusions. These authors suggested that this may be due to the use of lower doses to achieve the same steady state concentrations when compared to intermittent infusion dosing.[13]

A retrospective, single center observational study conducted from 2004 to 2008 evaluated the influence of vancomycin dose, serum trough concentrations, and dosing strategy on the evolution of acute kidney injury in critically ill patients. Vancomycin was prescribed for 303 patients during the study period, and 251 patients received vancomycin for > 96 hours. A total of 158 patients prescribed vancomycin were included in the retrospective analysis. Patients included in the study had a median age of 57 years and mean APACHE II scores of 21.32 ± 7.4; 66% were males. Most patients (91.8%) received intermittent vancomycin infusions for a mean treatment duration of 158 hours. Fourteen patients developed new onset AKI after vancomycin treatment, ten of these patients also received other nephrotoxic drugs during vancomycin treatment, and 12 later died in the ICU. There were no significant differences in the development of new onset AKI and duration of vancomycin treatment; the median duration of vancomycin therapy was175.5 hours (IQR 127.75-374.57). Patients with severe illnesses on admission, such as sepsis (64.3% versus 36.1%, p=0.047) or ischemic heart disease (35.7% versus 11.1%, p=0.023), were more likely to develop AKI. A vancomycin trough level of 16.5 mcg/dL was found to be the threshold for new onset AKI by receiver operating curve characteristic analysis (sensitivity=0.93 and specificity=0.60). Significant independent predictors of new onset AKI were the mean trough vancomycin concentration (OR=1.1174, p=0.024) and the APACHE II score (OR=1.141, p=0.012). Simultaneous use of aminoglycosides was the only nephrotoxic agent that was a significant predictor of new onset AKI (OR=18.896, p=0.002). Their multivariable analysis showed that continuous infusion with vancomycin was less likely to cause nephrotoxicity. The results in this study are consistent with previous studies which noted that elevated vancomycin trough levels are associated with nephrotoxicity. These results also suggest that patients who used nephrotoxic agents and vancomycin concurrently had 18.89 (p=0.002) greater odds of developing AKI than those who did not. Using univariate analysis, higher peak, mean, and initial vancomycin trough concentrations were associated with AKI; however, only the mean concentration was found to be an independent predictor of new onset AKI in regression modeling (OR, 1.174, p=0.024). The APACHE II score was identified as a significant independent predictor of new onset AKI, and a one unit increase in APACHE II score was associated with a 14.1% increase in the odds of AKI. The limitations of this study include its inability to account for all potential confounders due to the inherent limitations of a retrospective study design, a relatively small sample size which might not capture all predictive factors, and the exclusion of patients with increased serum creatinine at baseline.[14]

In 2010, Man and colleagues did a systematic review comparing the safety and efficacy of continuous and conventional intermittent infusions of vancomycin. Nine studies with small sample sizes were included in this systematic review. Since the studies included in the review were heterogeneous and provided limited data to support the use of continuous infusions of vancomycin, theses authors concluded that continuous infusions of vancomycin for multidrug resistant Gram positive infections might not be better than intermittent infusions. Additionally, they reported that continuous infusions did not appear to be more cost effective than intermittent infusion dosing.[15] A prospective multicenter randomized study which compared continuous versus intermittent infusions of vancomycin in severe Staphylococcal infections did not show any difference in renal function between the groups and concluded that any differences or changes in serum creatinine levels may indicate failure of therapy rather than vancomycin nephrotoxicty.[16]

The information below provides general dosing guidelines for vancomycin. A maintenance regimen of 15-20 mg/kg/dose with the frequency determined by current creatinine clearance is the accepted dosing method. There is no clinical utility of peak se-

rum concentrations, and therefore these should not be routinely measured. Serum trough concentrations should be routinely measured and serve as a surrogate indicator of the AUC: MIC ratio.[1] Dosing in renal impairment requires changes in dosing and monitoring methods and often requires a detailed reference source and nephrology consultation. Although vancomycin has been associated with nephrotoxicity and acute kidney injury, causality has not been confirmed, especially in complex critically ill patients. A prospective randomized double blind trial would potentially clarify this important concern.

UMC HEALTH SYSTEM

Adult Vancomycin Guidelines

I. Empiric Dosing for Vancomycin

***Loading* dose based on Total Body Weight (TBW)**

- Dose= mg/kg (TBW)
- Indicated in seriously ill patients or in those with high trough goals
- Loading dose: 25-30 mg/kg x **1 dose (max 3 g)**

***Maintenance* dose based on Total Body Weight (TBW)**

- Maintenance dose: 15-20 mg/kg **(initial max 2 g)**
- Round dose to the nearest **100 mg**

Empiric *dosing interval* based on renal function

CrCl (mL/min)	Dosing Interval (hrs)
> 100	Q8hr
75-100	Q12hr
50-74	Q18hr
20-49	Q24hr
Dialysis	See Renal Dosing

*Q6h dosing interval generally not used *empirically*

II. Levels and monitoring

In most cases only monitoring **troughs** is necessary. Clinical utility of peak levels in unclear.

- Peak levels may be obtained in patients requiring high troughs (15-20 mcg/mL), morbidly obese and burn patients
  - Goal peak 30-40 mcg/mL
- Troughs should be drawn **within 30 minutes prior** to the **4th dose** (prior to the 3rd dose if dosing interval >24hr)
- Peaks should be obtained **1 hour** after the end of the infusion
- ***Random* levels should only be obtained in patients with severe renal insufficiency or those on dialysis***

Indication	Target Trough Range
UTI, skin wound/abscess	10-15 mcg/mL
Sepsis, bacteremia, osteomyelitis, pneumonia, endocarditis, MRSA	15-20 mcg/mL

*** Target trough levels should be >10 mcg/mL to avoid resistance***

- If trough within goal range, re-check trough weekly (*stable* patients)
- Recheck trough if there are *significant changes in renal function*
- If trough levels are not within goal range then change in dose and/or frequency may be necessary

For adjustments in dose and frequency pharmacy may be consulted

III. Renal Dosing

- In *critically-ill* patients with renal insufficiency the initial *loading dose* (25-30 mg/kg) should **not** be reduced
- Subsequent dosing is based on renal function and serum trough concentrations

CrCl	Dose	Frequency
CrCl > 50 mL/hr	15-20 mg/kg/dose (750-1500 mg)	Q8-12hr
CrCl 20-49 mL/hr	15-20 mg/kg/dose (750-1500 mg)	Q24hr
CrCl < 20 mL/hr	15-20 mg/kg/dose	>24hr Based on serum concentration

- For Q8-12hr dosing, peak and trough should be drawn with 4th dose
- For Q24hr dosing, peak and trough should be drawn with the 3rd dose
- For intervals > 24hr a ***random level*** should be drawn and patient should be re-dosed once ***random level*** falls < 15 mg/L

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