Vancomycin Exposure and Acute Kidney Injury Outcome: A Snapshot From the CAMERA2 Study

Jiajun Liu,[1,2,3] Steven Y. C. Tong,[4,5] Joshua S. Davis,[5] Nathaniel J. Rhodes,[1,2,3] and Marc H. Scheetz[1,2,3;] for the CAMERA2 Study Group[*]

[1]Midwestern University Chicago College of Pharmacy, Downers Grove, Illinois, USA, [2]Northwestern Memorial Hospital, Chicago, Illinois, USA, [3]Midwestern University Chicago College of Pharmacy Pharmacometrics Center of Excellence, Downers Grove, Illinois, USA, [4]Victorian Infectious Diseases Service, The Royal Melbourne Hospital, and Doherty Department University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, Victoria, Australia, and [5]Menzies School of Health Research, Charles Darwin University, Darwin, Australia

Among patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia from a prospective randomized clinical trial, acute kidney injury (AKI) rates increased with increasing vancomycin exposure, even within the therapeutic range. AKI was independently more common for the (flu)cloxacillin group. Day 2 vancomycin AUC ≥470 mg·h/L was significantly associated with AKI, independent of (flu)cloxacillin receipt.

Keywords. vancomycin; AUC; β-lactam; MRSA bacteremia; combination therapy; pharmacokinetics; toxicodynamics; acute kidney injury; nephrotoxicity.

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia results in significant mortality, morbidity, and health care cost [1]. Vancomycin is a first-line therapy to treat serious MRSA infections and is the single most commonly utilized antibiotic in hospital settings in the United States [2]. Given the frequent prescribing of vancomycin, delineating the exposure–nephrotoxicity relationship is imperative to prevent unnecessary kidney injury.

Clinical studies have demonstrated that vancomycin-associated acute kidney injury (AKI) prevalence ranges from 5% to 43% [3]. Newly revised vancomycin therapeutic monitoring guidelines recommend an exposure target based on 24-hour area under the concentration-time curve (AUC) of 400–600 mg·h/L (assuming minimum inhibitory concentration ≤ 1 mg/L) to maximize efficacy and safety, yet clinical data regarding the exposure–nephrotoxicity threshold remain sparse

[4–8]. While adding β-lactams to standard therapy for MRSA bacteremia may improve infection outcomes, increased rates of nephrotoxicity have been observed, primarily with data of vancomycin plus piperacillin-tazobactam before the CAMERA2 study [9–11]. The prospective CAMERA2 trial was stopped early by the data and safety monitoring board because of unbalanced kidney toxicity [10]. Therefore, we quantitatively assessed the vancomycin exposure–nephrotoxicity relationship on day 2 of vancomycin treatment in MRSA bacteremia patients from the CAMERA2 trial [10].

METHODS

CAMERA2 was a prospective, randomized, multicenter trial comparing the combination of (flu)cloxacillin with standard therapy against standard therapy alone for MRSA bacteremia [10]. For the primary analysis population of the current study, we included patients who received vancomycin with or without (flu)cloxacillin (flucloxacillin or cloxacillin) or cefazolin and excluded patients on dialysis at baseline or who had missing vancomycin concentrations. Clinical and pharmacokinetic (PK) data assessed included age, receipt of (flu)cloxacillin, vancomycin trough data, and AKI (modified RIFLE criteria and modified Kidney Disease: Improving Global Outcomes [KDIGO] criteria).

To obtain the posterior-predicted vancomycin levels and estimate exposure, a nonparametric Bayesian PK model was constructed using the *Pmetrics* package (version 1.5.2) for R, version 3.5.3 (R Foundation for Statistical Computing) [12]. Vancomycin trough levels were assumed to be drawn 15 minutes before the last vancomycin dose. If a level was drawn on days where no vancomycin was administered, 24 hours were iteratively added to assume trough timing from the preceding trough time point. Day 2 of vancomycin was defined as receipt of therapy postrandomization and entry into the CAMERA2 trial. Details on pharmacokinetic modeling can be found in "PK Modeling" in the Supplementary Data.

The relationship between vancomycin exposure and modified KDIGO (m-KDIGO) stage ≥1 AKI was assessed with a logistic model, controlling for age and receipt of (flu)cloxacillin ((flu)cloxacillin vs non-(flu)cloxacillin groups) in Stata, version 15 (StataCorp LLC, College Station, TX). A LOWESS function was fitted to individual probability predictions from the logistic model. Optimal discriminant analysis (ODA) was conducted using the *ODA* package (version 1.1.1) for R [13, 14] to identify optimal vancomycin AUC_{24-48h} cut-points according to the ordinal m-KDIGO stages transformed dichotomously. ODA is a binary, recursive partitioning tool to identify optimal categorical threshold for continuous variables. Odds ratio (OR) was

calculated for each discrete AUC cut-point/m-KDIGO category. Furthermore, sensitivity analyses were conducted for patients receiving (1) vancomycin plus (flu)cloxacillin vs vancomycin alone and (2) vancomycin plus cefazolin (n = 28) vs vancomycin alone.

RESULTS

Of 352 patients from the primary analysis population, 61 were excluded due to dialysis (n = 55) at baseline or missing vancomycin levels (n = 6). Thus, 291 patients were included ((flu)cloxacillin group, n = 115; non-(flu)cloxacillin group, n = 176, including 28 receiving vancomycin plus cefazolin) (Supplementary Figure 1). The overall median (interquartile range [IQR]) age was 64 (49–78) years, with a majority being male patients (65.6%). The median (IQR) baseline creatinine and eGFR were 0.97 (0.75–1.63) mg/dL and 71.8 (38.4–98.7) mL/min/1.73 m^2, respectively, and were similar across subgroups [15]. Fifty (17.2%) patients experienced AKI, as defined by m-KDIGO ((flu)cloxacillin group, n = 36; non-(flu)cloxacillin group, n = 14). On average (SD), each patient received 11 (4) doses of vancomycin and had 4 (1) trough concentrations obtained during the first 7 days postrandomization. Mean (SD) trough concentrations were 14.1 (7.5) µg/mL and 17.6 (8.6) µg/mL on days 1 and 2, respectively (Supplementary Table 1).

A 1-compartment clearance model was selected as the best-fit Bayesian PK model (PK Modeling, Supplementary Materials). Median AUC_{24-48h} (IQR) was 398.2 (292.2–505.7) mg·h/L. After controlling for age and receipt of (flu)cloxacillin, AUC_{24-48h} (P = .004) was significantly associated with AKI. Similar significant associations were also observed with AKI, as defined by modified RIFLE for the aforementioned analysis (AUC_{24-48h}, P = .001) (Supplementary Figure 2). As shown in Figure 1, a nonlinear relationship existed between probability of AKI against AUC_{24-48h} (AUC_{0-24h} shown in Supplementary Figure 3). Further, receipt of (flu)cloxacillin (OR, 4.8; 95% CI, 2.4–9.5) independently increased the likelihood of experiencing AKI compared with the non-(flu)cloxacillin group. In the ODA analysis, AUC_{24-48h} cut-points were found at 470.1 (OR, 2.7; 95% CI, 1.5–5.0), 496.1 (OR, 5.29; 95% CI, 2.2–12.7), and 525.5 (OR, 6.8; 95% CI, 2.2–21.1) mg·h/L for m-KDIGO stages ≥1, ≥2, and 3, respectively (Supplementary Table 2). Day 1 vancomycin exposure–nephrotoxicity relationships can be found in the Supplementary Data. Time-to-event analyses can be found in Supplementary Figure 4.

In the sensitivity analysis of the (flu)cloxacillin group vs vancomycin alone (n = 263) (Supplementary Figure 5), AUC_{24-48h} (P = .006) remained significant in the logistic models that controlled for age and receipt of (flu)cloxacillin (data not shown). Conversely, no statistical significance was observed for AUC_{24-48h}
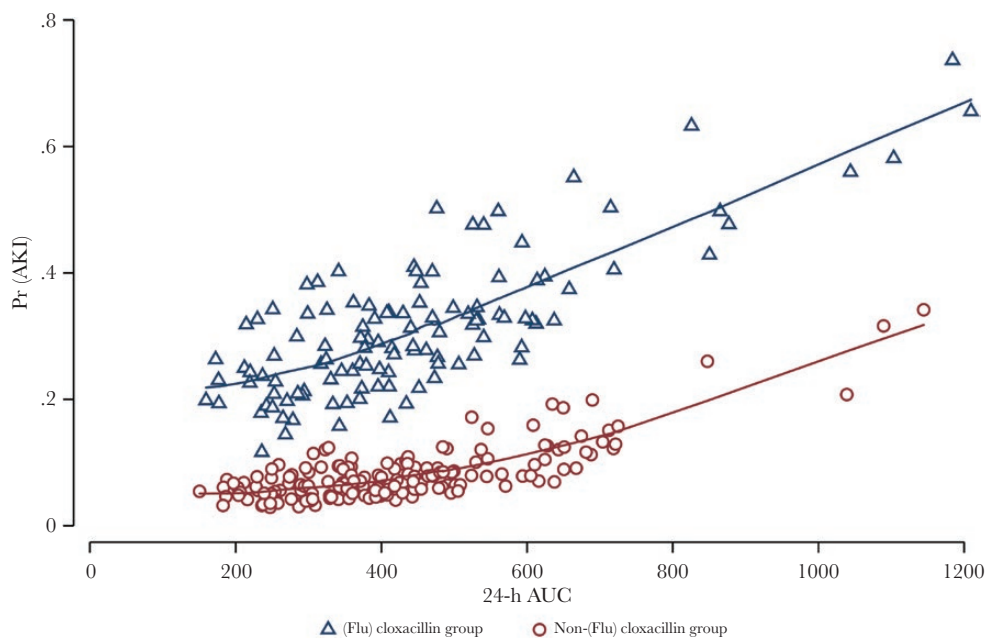

Figure 1. Day 2 vancomycin exposure–toxicity relationships (stratified by (flu)cloxacillin vs non-(flu)cloxacillin groups). Pr(AKI), probability of Stage 1 AKI as defined by modified KDIGO per the parent study (ie, CAMERA2): Stage 1 is serum creatinine 1.5–1.9 times baseline in the first 7 days (OR ≥26.5 µmol/L increase from baseline in the first 48 hours); Stage 2 is serum creatinine 2.0–2.9 times baseline in the first 7 days; Stage 3 is serum creatinine ≥3.0 times baseline in the first 7 days (OR ≥353.6 µmol/L increase from baseline in the first 48 hours OR new initiation of renal replacement therapy within 90 days). Urine output criteria were not included as data on urine output were not collected; analysis population, n = 291; solid lines represent LOWESS function for respective groups. Abbreviations: AKI, acute kidney injury; AUC, area under the concentration-time curve; Pr(AKI), probability of Stage 1 AKI.

Figure 2. Day 2 vancomycin exposure–toxicity relationships (stratified by vancomycin plus cefazolin vs vancomycin alone). Analysis population, n = 176; solid lines represent LOWESS function for respective groups. Abbreviations: AKI, acute kidney injury; AUC, area under the c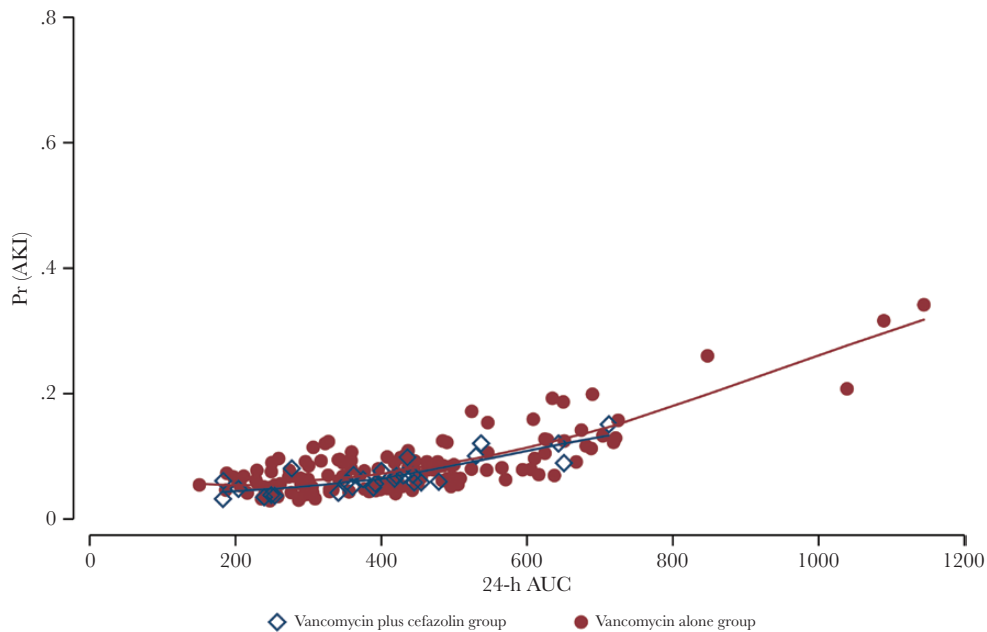oncentration-time curve; Pr(AKI), probability of Stage 1 AKI as defined by modified KDIGO criteria as detailed in Figure 1.

(P = .60) in vancomycin alone vs vancomycin plus cefazolin (Figure 2; AUC_{0-24h} shown in Supplementary Figure 6).

DISCUSSION

We assessed the vancomycin exposure–nephrotoxicity relationship and demonstrated that day 2 vancomycin exposure was significantly associated with nephrotoxicity. The risk of vancomycin-associated kidney injury was relatively flat until an AUC_{24-48h} of ~300 mg·h/L, after which linear increases were observed, for both vancomycin alone and vancomycin with (flu)cloxacillin. While such relationships have been well described previously, our findings are important because they were sourced from a prospective study, and we demonstrated increasing rates of AKI within the therapeutic range for vancomycin [5, 6, 8]. While there is a certain risk of AKI within the recommended AUC range of 400–600 mg*24h/L, these data suggest that the vancomycin target concentrations need to undergo continued scrutiny in order to find the safest exposures that are still associated with efficacy for serious MRSA infections [4].

Our analysis is consistent with reported results from the parent trial [10]. Receipt of vancomycin and (flu)cloxacillin increased the risk of AKI as compared with vancomycin alone. Further, when combination therapy or vancomycin alone was considered, we found early (ie, days 1 and 2) vancomycin AUC cut-points to be associated with increasing ordinal scale kidney injury. While there is consistency of findings (ie, increasing AUC was associated with worse kidney outcomes), our primary

analysis was based on m-KDIGO stage 1. Such an absolute threshold (as opposed to percent changes) has been proposed to better detect early AKI across the heterogeneity of baseline kidney disease [16].

Recent studies have attempted to discern the vancomycin AUC–toxicity threshold for AKI. An in vivo rat study by Avedissian and colleagues examined exposure–toxicity relationships for vancomycin-induced AKI using urinary biomarkers [17]. Twenty-four-hour AUC (mg·h/L) of 482.2 was associated with 90% maximal rise of kidney injury molecule 1 on day 1, indicating early proximal tubule injury associated with AKI. Quantitatively, the thresholds for injury agree, though the timeline differs (eg, CAMERA2 patients who experienced m-KDIGO AKI reached that end point after a mean of 4.5 days) (data not shown). This may be due to rats receiving higher doses to achieve allometry or the use of a more sensitive and earlier marker of kidney injury [18]. Suzuki and colleagues investigated AKI (0.5 mg/dL or a 50% increase in serum creatinine) in patients receiving vancomycin. Patients with AKI had a higher mean AUC_{0-24h} (mg·h/L) of 600–800 vs those without (mean AUC_{0-24h}, 400–600; P = .014) [5]. Similar to our study, this study demonstrated a gradient effect; however, the high exposures could be driven by aggressive dosages to target MRSA pneumonia. Zasowski and colleagues retrospectively observed an increased relative risk of nephrotoxicity at the following cut-points (AUC_{0-24h} and AUC_{24-48h} ≥ 677, AUC_{0-48h} ≥ 1218) [6]. Notably, patients experiencing nephrotoxicity in this study appeared to be critically ill (median APACHE II, 20.5) with baseline renal disease and had relatively high median vancomycin

exposure on days 1 and 2. Further, it should be noted that their cut-points were based on a 3- to 5-fold increase. More recently, Lodise and colleagues conducted a prospective, multicenter trial of patients with MRSA bacteremia and demonstrated that an AUC_{24-48h} (mg·h/L) of 793 was associated with the highest AKI risk compared with AUC_{24-48h} ≤343 [7]. Additional work from that study is ongoing to understand incremental relationships between vancomycin exposure and AKI [19].

Consistent with studies from others, we found that AUC_{24-48h} in our exposure–response analysis was the best predictor of AKI [6, 7]. Day 2 is close to steady-state conditions for many receiving vancomycin therapy, and dosing has stabilized for those receiving therapeutic drug monitoring after the first day. Nevertheless, in order to ensure that our findings were not just intermediate variables in the causal pathway (given decreased GFR leads to increased vancomycin AUC), we estimated day 1 AUC as well (Supplementary Tables 1 and 2). Indeed, we also found a gradient effect across the AUC_{0-24h} cut-points for AKI on day 1, though the magnitude of effect was smaller at these thresholds. This demonstrates that AUC_{0-24h} may serve as an early time point for clinical decisions, but more studies with sensitive biomarkers of AKI are needed in patients to confirm this hypothesis.

While some studies suggest that the addition of β-lactam to standard therapy may lead to fewer MRSA bacteremia treatment failures, the clinical benefit has not been clearly demonstrated. Furthermore, various combination therapies have been associated with an increased risk of AKI [9–11, 20]. For drugs that are active against methicillin-susceptible *Staphylococcus aureus*, (flu)cloxacillin and piperacillin-tazobactam have been associated with increased serum creatinine when paired with vancomycin. For piperacillin-tazobactam, controversy exists as to whether serum creatinine rise defines AKI in these patients [21, 22]. Our study showed gradient effects for vancomycin exposure whether or not (flu)cloxacillin was given. Future mechanistic studies are warranted.

Our results have limitations. As a pragmatic clinical trial, vancomycin concentrations were measured and reported at each individual study site as part of a clinical efficacy study that was not designed specifically to calculate AUC exposures. However, all laboratories were accredited clinical laboratories, and study sites followed protocol for trough collection and adjustment of doses. Our analysis employed a 1-compartment model that was adjusted for kidney function and body weight. While only troughs existed, each subject had an average of 4.2 troughs collected. Thus, repeated measures allowed for improved patient-specific model fitting (within the confines of the available data). To this end, the PK model bias and imprecision were reasonably low (–0.10 and 0.518, respectively). Our study is further strengthened by the prospective, randomized design, with 27 study sites across multiple countries. Trials with richer PK sampling designs are ultimately warranted to confirm study results.

In conclusion, increasing vancomycin exposure, even within the therapeutic range and regardless of concomitant use of (flu) cloxacillin, is associated with increasing probability of AKI. Additional work to fully understand the therapeutic window is warranted.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author/s:
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