1568. The Pharmacodynamic–Toxicodynamic Relationship of AUC and CMAX in Vancomycin-Induced Kidney Injury

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Background. Vancomycin induces exposure-related acute kidney injury [AKI]; yet the toxicodynamic (TD) driver for toxicity (area under the curve [AUC], vs. maximum concentration [CMAX] vs. trough concentrations [CMIN]) remains unclear. Recent vancomycin guidelines now recommend monitoring AUC over troughs. Here we employed our translational rat model with intensive dose fractionation and sensitive FDA qualified urinary biomarkers to better understand TD relationship.

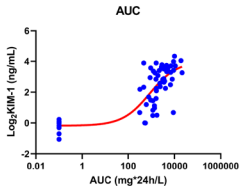
Methods. Male Sprague-Dawley rats received intravenous (IV) vancomycin via an internal jugular vein catheter. Total daily doses of 300 and 400 mg/kg/day were administered as a single, twice, thrice and four times a day injection over 24 hours. Controls received IV saline. Plasma sampling was conducted via a second dedicated jugular catheter, with up to 8 samples in 24 hours. Twenty-four-hour urine was collected during this time and assayed for kidney injury molecule 1 (KIM-1) and other urinary biomarkers using the MILLIPLEX MAP Rat Kidney Panel. Vancomycin in plasma was quantified via LC-MS/MS. PK analyses were conducted using Pmetrics for R. PK exposures during the first 24 hours (i.e., $AUC_{0\text{-}24hours}$, $CMAX_{0\text{-}24hours)}$ were calculated from Bayesian posteriors. Pharmacokinetic-toxicodynamic (PK-TD) relationships were assessed with the best fit mathematic model (e.g., exposure-response curve fitting in GraphPad v.7).

Results. Sixty-four vancomycin treated and control rats contributed to PK-TD data. An exposure-response (via 4-parameter Hill) model was identified for $AUC_{0\text{-}24hours}$ vs KIM-1 (R^2 = 0.62, Figure 1a). Convergence was not obtained for exposure-response models for $CMAX_{0\text{-}24hours}$ and CMIN, which was also verified visually (Figure 1b and c). Despite the intensive fractionation, $AUC_{0\text{-}24hours}$ and $CMAX_{0\text{-}24hours}$ were highly correlated ($P < 0.001$, rho = 0.89) and this correlation was consistent across KIM-1 values (Figure 2).

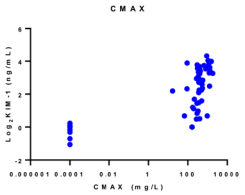
Conclusion. Vancomycin-induced kidney injury was driven by $AUC_{0\text{-}24\ hours}$ and not CMIN. Continuous infusion studies are needed to understand if changing the infusion profile can improve safety; however, these studies suggest that isometric AUCs may result in similar toxicity. When using intermittent infusion schemes, clinicians should focus on AUC to prevent AKI.

Figure 1. 4-parameter Hill fit for (a) Log_2 KIM-1 vs. Log_{10} $AUC_{0\text{-}24hrs}$ and (b) Log_2 KIM-1 vs. Log_{10} $CMAX_{0\text{-}24hrs}$ and (c) CMIN vs. KIM-1

a).



b).



c).

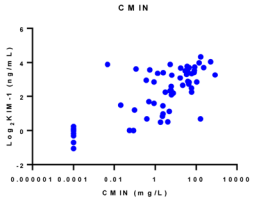
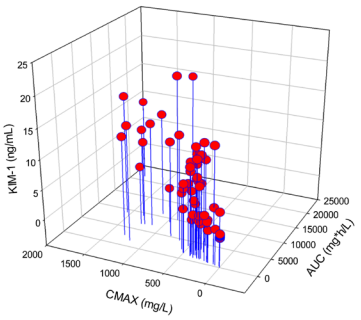


Figure 2. 3D-Scatter Plot of KIM-1(z-axis), $AUC_{0\text{-}24Hrs}$ (x-axis) and $CMAX_{0\text{-}24Hrs}$ (y-axis) for all 64 Animals



Disclosures. **All authors:** No reported disclosures.

1569. A Translational Model to Assess the Impact of Polymyxin B Dose Fractionation on Kidney Injury

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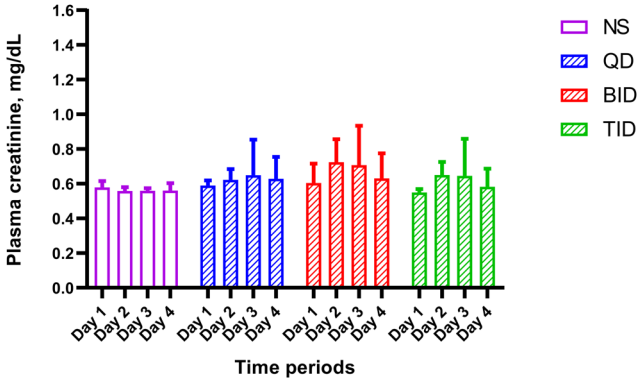
Background. Progression of antimicrobial resistance has revived Polymyxin B (PB) use in clinical practice. Dose-dependent acute kidney injury (AKI) limits its clinical use. It is unclear whether dose fractionation of total daily dose can lessen kidney injury. We assessed the role of PB fractionation on AKI in a translational model that employs sensitive urine biomarkers qualified by the FDA.

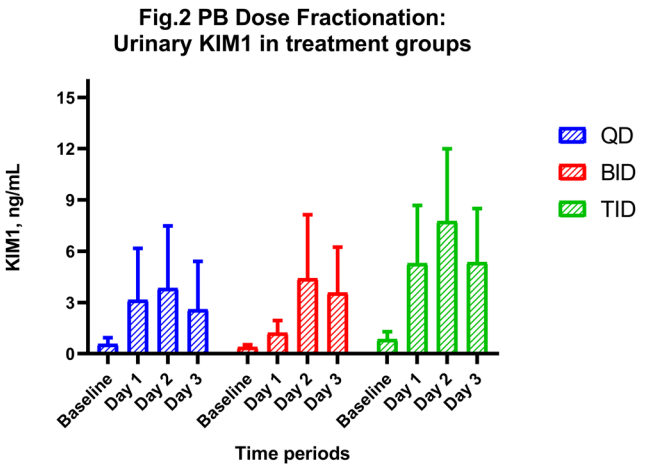
Methods. Male Sprague–Dawley rats received 12 mg/kg/day PB subcutaneously for 3 days or equal-volume normal saline (NS). PB was administered in 3 separate fractionated daily doses: 12 mg/kg daily (QD), 6 mg/kg twice daily (BID), and 4 mg/kg thrice daily (TID). Staggered blood sampling was done on days 1 to 4 and 24 hour urine was collected at baseline, on days 1, 2, and 3. Plasma creatinine (Cr) was quantified using LCMS/MS, and 24 hour urinary biomarkers (KIM1, OPN, CLN, calbindin, GSTα, IP-10, TIMP-1, and VEGF) were assayed with MILLIPLEX Rat Kidney Toxicity Magnetic Bead Panel. Mixed-effects models were used.

Results. A total of 32 rats contributed to the study data. Mean Cr were constant across groups over time (Figure 1, P = 0.18). For NS group, all biomarkers remained at baseline throughout study. Significant differences were seen for fractionation schemes for KIM1 (P = 0.02), CLN (P = 0.03), IP-10 (0.007) and TIMP-1 (P = 0.04). The differences for KIM1, IP-10, and TIMP-1 were driven by higher observed values in TID than those of BID as early as day 1 ($P < 0.04$). Furthermore, CLN was elevated for TID when compared with BID at baseline (P = 0.048). Similarly, TID group had the highest (but non-significant) elevations for IP-10 and TIMP-1 compared with QD on study days. Amongst all urine biomarkers, KIM1 in TID exhibited the most rapid rise from baseline to day 2 (Figure2, $P < 0.0001$).

Conclusion. In this translational model in which a single total daily dose was fractionated, sensitive urinary biomarkers indicated that TID dosing was worse than BID or QD dosing; dose fractionation of PB may lead to increased AKI. In addition, KIM1 rose rapidly as an early marker for AKI. Further efforts are needed to investigate the PK-TD relationship of PB in order to decrease AKI.

Fig.1 PB Dose Fractionation: Plasma creatinine in treatment groups





Disclosures. **All authors:** No reported disclosures.

1570. Association Between Vancomycin Area Under the Curve (AUC) and Nephrotoxicity

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Background. It is unclear whether increased vancomycin area under the curve (AUC) contributes to acute kidney injury (AKI) risk.

Methods. This retrospective cohort study was undertaken to determine whether vancomycin AUC > 550 is associated with a higher rate of AKI than an AUC < 550. Patients treated with vancomycin for at least 4 days at the St. Louis VA from 1/1/2016–9/31/2018 were included. The primary outcome was AKI (defined as an increase in serum creatinine by 0.3 mg/dL or 50% from baseline). Secondary outcomes included length of stay, readmission, or mortality in 30 days, AKI rate with concurrent antibiotics, and AKI rate with comorbidities. The AUC was calculated as daily dose (in mg) divided by vancomycin clearance. The variables of age ≥ 70, vancomycin AUC ≥ 550, creatinine clearance (CrCl) < 50 mL/minute, concomitant antibiotic administration, vancomycin treatment ≤ 7 days, and the presence of comorbidities were included in a bivariate analysis. Variables with a *P*-value of <0.2 were included in a multivariate logistic regression model.

Results. Two hundred patients were included in the analysis; 100 patients with an AUC ≥ 550, and 100 with an AUC < 500. Only mean vancomycin dose (1722.50 mg vs. 2361.25 mg; $P < 0.05$), mean AUC (465.88 vs. 696.45; $P < 0.05$), and peak SCr (1.22 mg/dL vs. 1.48 mg/dL; $P = 0.015$) were significantly different between groups; AUC < 550 vs. AUC ≥ 550, respectively. Acute kidney injury occurred in 22% (44/200) of all patients; 42% (42/100) with a calculated AUC ≥ 550 developed AKI compared with 2% (2/100) of patients with an AUC < 550 ($P < 0.05$). The secondary outcomes of concomitant nephrotoxic agents, length of stay, readmission at 30 days, and 30-day mortality were not significantly different between groups. Only age ≥ 70, vancomycin AUC ≥ 550, CrCl < 50 mL/minute, concomitant piperacillin–tazobactam administration, and the presence of comorbidities were included in the multivariate regression. Age ≥ 70, CrCl < 50 mL/minute, and AUC ≥ 550 [OR 49.5 (95% CI 10.1 – 242.3; $P < 0.05$)] were found to be independently associated with risk for developing AKI.

Conclusion. Patients with a calculated vancomycin AUC ≥ 550 were found to have a significantly higher rate of AKI compared with those with an AUC < 550.

Disclosures. **All authors:** No reported disclosures.

1571. Evaluation of a Single Post First Dose Vancomycin Level to Achieve a Goal Vancomycin AUC

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Background. The 24-hour area under the serum concentration–time curve (AUC24) is the most defensible measure to predict the effectiveness and toxicity of vancomycin. The optimal method and time point to assess and optimize AUC24, however, have yet to be determined. Measuring a trough concentration at steady state has been the traditional method of monitoring vancomycin, but trough is unreliable at estimating AUC24. More accurate methods for estimating AUC24 are paired sample analysis, or a single optimally timed sample combined with population pharmacokinetics. We wished to optimize AUC24 prior to steady state for earlier goal attainment, thereby decreasing risk of treatment failure, resistance, and/or nephrotoxicity. A single optimally timed single post first dose level may be used to estimate drug clearance and thereby AUC. Based on the post first dose concentration and a population pharmacokinetic model, clearance is calculated, and the dosing regimen can be adjusted to achieve a desired AUC24. Our institution has enabled pharmacists to obtain post first dose vancomycin levels and make early dose adjustments. The aim of this project is to monitor the accuracy of this method and the outcomes of patients who have received post first dose vancomycin levels and subsequent dose assessment/adjustment.

Methods. Single-center cohort study via electronic chart review of patients with vancomycin therapeutic dose monitoring based on post first dose vancomycin levels obtained between January 2019 and April 2019.

Results. 41 patients were dosed and monitored based on post first dose vancomycin levels. Fourteen patients (34%) required dose adjustments based on the post first dose level. Accuracy of assessment was determined in 15 patients (37%) via a steady-state level used to measure vancomycin clearance and AUC24. At steady-state following dose assessment 14/15 (93%) patients had desired targeted goal AUC24. Only two patients (5%) had greater than a 50% increase in baseline serum creatinine.

Conclusion. Post first dose-level analysis resulted in dose regimen modifications in one-third of patients. This consistently allowed the attainment of goal AUC24 at steady-state.

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1572. Evaluation of Vancomycin Levels Following Weight-Based Pre-operative and Re-warming Vancomycin Dosing in Cardiac Surgery

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Background. Weight-based dosing of vancomycin in the pre-operative setting is standard practice at our institution based on the 2013 Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery. Our antimicrobial subcommittee recommended a weight-based dosing (15 mg/kg/dose) approach to negate the need for a subsequent vancomycin dose during rewarming in cases requiring cardiopulmonary bypass (CPB). However, after discussion with all perioperative stakeholders, administration of vancomycin 1 g intravenously for all patients on CPB at rewarming continued. The aim of this study was to determine whether subsequent rewarming vancomycin doses contributed to the development of postoperative acute kidney injury (AKI).

Methods. This was a prospective cohort study of all cardiac surgery patients undergoing surgery from April 16, 2018 through April 27, 2018 for the development of AKI as defined by RIFLE criteria. Institutional guidelines recommend vancomycin as perioperative prophylaxis in all cardiac surgery cases with a preoperative 15 mg/kg dose, a 1 g rewarming dose, and nomogram-based post-operative dosing. Vancomycin troughs were obtained prior to the first post-operative dose in the intensive care unit. Serum creatinine was recorded on the post-op day (POD) 0, POD 1, and POD 7.

Results. Data were collected on 54 patients over a 2-week period. The median age was 64 years of age, with 41 (76%) male patients. Seven patients (13%) had a prior diagnosis of chronic kidney disease (CKD). Post-op AKI developed in 8 patients (15%) by POD 7; two of which had CKD at baseline. All patients received appropriate preoperative and postoperative dosing. Forty-nine (91%) patients had trough levels obtained, with the median trough 7.6 µg/mL (range 2 – 15.9 µg/mL) prior to the first nomogram-based post-operative vancomycin dose. Higher rates of AKI were associated with a longer duration of CPB rather than vancomycin levels obtained.

Conclusion. The current practice of redosing 1 g vancomycin at rewarming did not appear to contribute higher rates of AKI. In addition, all vancomycin trough levels reviewed were less than 20 µg/mL. Levels observed in this study are lower than previously described in the literature to cause nephrotoxicity. Further evaluation of vancomycin use in this setting is warranted

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1573. Population Pharmacokinetic Analyses for Cefepime in Adult and Pediatric Patients

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Background. Cefepime (CEF) is commonly used for adult and pediatric infections. Several studies have examined CEF's pharmacokinetics (PK) in various populations; however, a unifying PK model for adult and pediatric subjects does not yet exist. We developed a combined population model for adult and pediatric patients and validated the model.