JPPT | Single-Center Retrospective Study

# Comparison of Vancomycin Trough–Based and 24-Hour Area Under the Curve Over Minimum Inhibitory Concentration (AUC/MIC)–Based Therapeutic Drug Monitoring in Pediatric Patients

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**OBJECTIVES** Vancomycin 24-hour area under the curve over minimum inhibitory concentration (AUC/MIC) monitoring has been recommended over trough-based monitoring in pediatric patients. This study compared the proportion of target attainment between vancomycin AUC/MIC and trough-based methods, and identified risk factors for subtherapeutic initial extrapolated targets.

**METHODS** This was a retrospective, observational study conducted at KK Women's and Children's Hospital (KKH), Singapore. Patients aged 1 month to 18 years with stable renal function who received intravenous vancomycin between January 2014 and October 2017, with at least 2 vancomycin serum concentrations obtained after the first dose of vancomycin, were included. Using a pharmacokinetic software, namely Adult and Pediatric Kinetics (APK), initial extrapolated steady-state troughs and 24-hour AUC were determined by using a one-compartmental model. Statistical tests included Wilcoxon rank sum test, McNemar test, logistic regression, and classification and regression tree (CART) analysis.

**RESULTS** Of the 82 pediatric patients included, a significantly larger proportion of patients achieved therapeutic targets when the AUC/MIC-based method (24, 29.3%) was used than with the trough-based method (9, 11.0%; $p < 0.01$). Patients with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 $m^2$ or with age <13 years had an increased risk of obtaining subtherapeutic targets. However, empiric vancomycin doses of 60 mg/kg/day would be sufficient to achieve serum therapeutic targets, using the AUC/MIC-based method.

**CONCLUSION** The AUC/MIC-based vancomycin monitoring may be preferred because a larger proportion of patients could achieve initial therapeutic targets. Future prospective studies with larger sample size will be required to determine the optimal vancomycin strategy for pediatric patients.

**ABBREVIATIONS** APK, Adult and Pediatric Kinetics program; ASHP, American Society of Health-System Pharmacists; AUC/MIC, area under the curve over minimum inhibitory concentration; CART, classification and regression tree analysis; eGFR, estimated glomerular filtration rate; KKH, KK Women's and Children's Hospital, Singapore; MRSA, methicillin-resistant *Staphylococcus aureus*; pRIFLE, Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease; TDM, therapeutic drug monitoring

**KEYWORDS** pediatric; therapeutic drug monitoring; vancomycin

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## Introduction

Therapeutic drug monitoring (TDM) of vancomycin is recommended because of its narrow therapeutic window.[1] Traditionally, vancomycin trough serum concentrations have been used as a surrogate to the area under the curve over minimum inhibitory concentration (AUC/MIC) ratio, because it was the most practical method of monitoring the efficacy of vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) infections in clinical practice.[2]

There are several limitations associated with the use of vancomycin trough serum concentrations. Firstly, vancomycin troughs represent a single exposure point at the end of a dosing interval, hence are unlikely to accurately predict the concentration time profile during the treatment course.[3] Secondly, vancomycin serum troughs have wide interindividual and intraindividual variability, making it difficult to achieve a predefined target range.[4] Also, achieving therapeutic serum vancomycin troughs has not been consistently correlated

with improved clinical outcomes; hence, vancomycin trough monitoring might not be optimal.[3,5]

In pediatric patients, variability in vancomycin dosing and pharmacokinetic properties is enhanced by maturing glomerular filtration in the early childhood years.[6] Nephrotoxicity has been associated with serum vancomycin troughs greater than 15 µg/mL in pediatric patients.[7] Retrospective studies have also reported up to 80% to 90% of pediatric patients not being able to achieve therapeutic serum vancomycin trough concentrations at steady-state, when vancomycin was initiated at guideline-recommended doses according to age.[8–10]

Newer data suggest that serum vancomycin troughs might not correlate well with AUC/MIC, especially in the pediatric population. Ploessl et al[11] reported no correlation between vancomycin trough concentrations and AUC/MIC ($r$ = 0.082, p = 0.07) in 40 pediatric patients. In pharmacokinetic studies, serum vancomycin trough concentrations of 7 to 10 µg/mL were more predictive of achieving an AUC/MIC ≥400 in MRSA-infected children with an MIC of 1 µg/mL.[12] Thus, in the latest vancomycin consensus guidelines, AUC/MIC monitoring is recommended for vancomycin in both adult and pediatric patients.[1] A target AUC/MIC of 400 to 600 is recommended for serious MRSA infections, and vancomycin serum concentrations should be obtained within 24 to 48 hours of vancomycin therapy.[1]

In view of the latest recommendations for vancomycin AUC/MIC monitoring,[1] as well as the uncertainty of whether vancomycin AUC is well correlated to clinical efficacy and toxicity,[13] this research aims to study vancomycin dosing and TDM practices in pediatric patients by comparing the 2 TDM methods using the APK (Adult and Pediatric Kinetics) software. The vancomycin trough-based and AUC/MIC-based method will be compared, to assess differences in proportions of target attainment, risk factors for subtherapeutic target attainment, clinical outcomes, and empiric dose recommendations.

## Materials and Methods

**Study Design.** This was a single institution, retrospective, observational study conducted at KK Women's and Children's Hospital, Singapore (KKH), an 850-bed tertiary-care hospital specializing in women's and children's health.

**Study Population.** This study included pediatric patients aged 1 month to 18 years with stable renal function. These patients received intravenous vancomycin at KKH between January 1, 2014, and October 31, 2017, and had at least 2 serum vancomycin concentrations obtained after the first dose of vancomycin. Stable renal function was defined as ≤25% change in estimated glomerular filtration rate (eGFR), using the bedside Schwartz equation over the past 3 months; or if no known history of renal disease, then assumed stable.[14,15] Those on dialysis, extracorporeal membrane oxygenation, or with acute kidney injury prior to initiating vancomycin were excluded from the study. Patients on vancomycin for surgical prophylaxis and infants younger than 44 weeks' post-menstrual age were also excluded. For patients who had more than 1 course of vancomycin during their hospital stay, only the first course was included.

**Dosing and TDM Practices at KKH.** At KKH, intravenous vancomycin was initiated at 60 mg/kg/day equally divided every 6 hours on the basis of actual body weight (maximum 4 g/day) and infused over 1 hour. When vancomycin was initiated, recommendations for vancomycin TDM would be provided by pharmacists (see Supplemental Figure S1). The first serum vancomycin concentration would be obtained 1 hour after the end of the first dose infusion, and the second vancomycin concentration would be obtained just before the second dose.[16] This practice of obtaining serum vancomycin concentrations after the first-dose drug infusion was initiated in all pediatric patients on vancomycin in October 2013, for rapid attainment of target concentrations, and to minimize the duration of suboptimal antibiotic exposure to prevent the development of antibiotic resistance.[17]

The 2 serum vancomycin concentrations obtained above would be entered into a pharmacokinetics program, APK (Creighton University, Omaha, NE). The 24-hour AUC is estimated by using the log-linear trapezoidal method in APK, which is recognized to yield similar AUC estimations compared with the guideline-recommended Bayesian AUC estimation.[1,18] The program also derives patient-specific pharmacokinetic parameters using the Sawchuk-Zaske method (one-compartmental linear pharmacokinetics model, equations listed in Supplemental Table S1), which has been validated in both adults and pediatric patients.[19–22] A preliminary investigation validating the APK software in our institution in 20 patients showed that median difference between actual and extrapolated serum vancomycin troughs was 18.2% (IQR, 7.8–25.6), which is comparable to other pharmacokinetic programs.[23,24] Hence, APK enables steady-state vancomycin peak, trough serum concentrations, and 24-hour AUC to be estimated. Using the estimated 24-hour AUC or vancomycin serum troughs, the optimal dose of vancomycin would be predicted by APK (see Supplemental Table S2).

In this study, the target AUC/MIC for vancomycin in pediatric patients is 400 to 600.[1] Target extrapolated steady-state serum vancomycin troughs for pediatric patients at KKH were obtained from the 2009 ASHP (American Society of Health-System Pharmacists) vancomycin guidelines.[2] Target troughs of 15 to 20 µg/mL were recommended for complicated infections including methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia; and 10 to 15 µg/mL for all other infections.[2]

**Study Objectives.** The primary objective of this study was to compare the proportion of target attainment between vancomycin AUC/MIC and trough-based TDM methods.

Secondary objectives include 1) comparing risk factors for subtherapeutic initial extrapolated vancomycin troughs with AUC/MIC; 2) comparing the proportion of patients with treatment success and nephrotoxicity in the therapeutic and nontherapeutic groups, using the 2 TDM methods; and 3) comparing the initial adjusted vancomycin dose required to achieve therapeutic vancomycin troughs and AUC/MICs.

**Definitions.** The initial extrapolated serum vancomycin trough or AUC refers to the first steady-state vancomycin trough or 24-hour AUC extrapolated from APK from the empiric dose of intravenous vancomycin administered (Supplemental Table S2). For evaluation of clinical outcomes, only patients with positive bacterial cultures and on vancomycin therapy were analyzed. Treatment success was defined as a composite outcome of 1) clinical success determined on day 7 following the first positive culture if the patient was afebrile for at least 48 hours (temperature <38°C), was hemodynamically stable without need for vasopressors, and had no tachycardia; 2) microbiologic clearance, defined by documented or presumed eradication of the baseline pathogen; and 3) lack of 30-day all-cause in-hospital mortality from the start of vancomycin therapy.[25] Vancomycin-associated nephrotoxicity was based on the Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) serum creatinine criteria after initiation of vancomycin, persisting for ≥2 consecutive days, within 72 hours of completion of therapy.[26,27]

Patient-specific vancomycin MIC values were not available because the institution's microbiology laboratory uses disk diffusion tests to determine vancomycin susceptibility. Thus, vancomycin MIC values were assumed to be 1 µg/mL for all patients.[1,28,29]

**Data Collection.** The list of patients who fulfilled the inclusion and exclusion criteria was extracted from the electronic medical records system. Parameters collected include patient's age, weight, height, indication for vancomycin, serum creatinine, underlying comorbidities, prior (30 days before) and concurrent use of nephrotoxic agents (listed in Table 1), initial and first adjusted vancomycin dose and frequency, fever, microbial cultures, and 30-day all-cause in-hospital mortality.[30]

**Statistical Analyses.** All patients who met the inclusion and exclusion criteria were analyzed. The Kolmogorov-Smirnov test was done to test continuous data for normality.[31] When comparing the serum vancomycin trough-based and AUC-based methods, continuous variables are presented as median and IQR, and analyzed by using Mann-Whitney *U* and Wilcoxon signed rank tests. Categorical data were compared by using chi-square test and McNemar test.

**Table 1.** Demographic and Clinical Characteristics of Pediatric Patients Receiving Vancomycin

| | Patients on Vancomycin (N = 82) |
|---|---|
| Sex, n (%) | |
| Male | 54 (65.9) |
| Female | 28 (34.1) |
| Race, n (%) | |
| Chinese | 43 (52.4) |
| Malay | 20 (24.4) |
| Indian | 8 (9.8) |
| Others | 11 (13.4) |
| Age, median (IQR), yr* | 4.7 (1.2–11.8) |
| Age group, n (%) | |
| <2 yr | 27 (32.9) |
| 2 to <6 yr | 18 (22.0) |
| 6 to <13yr | 21 (25.6) |
| ≥13 yr | 16 (19.5) |
| Weight, median (IQR), kg* | 15.5 (9.8–32.0) |
| Weight category, n (%) | |
| <25 kg | 53 (64.6) |
| 25 kg to <50 kg | 23 (28.1) |
| ≥50 kg | 6 (7.3) |
| Baseline eGFR, median (IQR), mL/min/1.73 m²* | 94.3 (77.7–109.0) |
| Underlying medical condition, n (%)† | |
| Cancer/stem cell transplant | 40 (48.8) |
| Gastrointestinal | 14 (17.1) |
| Cardiac | 8 (9.8) |
| Respiratory | 7 (8.5) |
| Neurologic | 7 (8.5) |
| Endocrine/renal | 5 (6.1) |
| None | 14 (17.1) |
| Others | 1 (1.2) |
| Concurrent or prior nephrotoxic agents, n (%)‡ | 78 (95.1) |
| Initial vancomycin dose, median (IQR), mg/kg/day* | 59.9 (59.2–60.1) |
| Indication by culture, n (%)§ | |
| Empiric use | 51 (62.2) |
| Targeted use | 31 (37.8) |
| Indication by site of infection, n (%) | |
| Blood and line | 52 (63.4) |
| Central nervous system | 13 (15.9) |
| Respiratory | 11 (13.4) |
| Skin, soft tissues, bone and joint | 4 (4.9) |
| Others | 2 (2.4) |
| Duration of vancomycin, median (IQR), days* | 4 (2–9.0) |

*eGFR, estimated glomerular filtration rate based on the modified Schwartz equation*

* All parameters had a non-normal distribution ($p < 0.05$) when the Kolmogorov-Smirnov test was performed.

† Patients may have more than 1 underlying medical condition.

‡ Defined by the use of nephrotoxic agents 30 days before and until the end of the vancomycin course. Nephrotoxic agents include nonsteroidal anti-inflammatory agents, aminoglycosides, acyclovir/ganciclovir, cidofovir, amphotericin B, calcineurin inhibitors, chemotherapy including methotrexate and cisplatin, diuretics, piperacillin-tazobactam, and polymyxin B.[30]

§ Indication stated for entire vancomycin course.

**Table 2.** Comparison of the Proportion of Nontherapeutic and Therapeutic Initial Extrapolated Vancomycin Trough With Calculated AUC/MIC

| | Extrapolated Vancomycin Trough Method (N = 82) | | AUC/MIC Method (N = 82) | | p Value* |
|---|---|---|---|---|---|
| | n (%) | Trough, Median (IQR), µg/mL | n (%) | AUC/MIC, Median (IQR) | |
| Subtherapeutic | 67 (81.7) | 5.9 (4.1–8.1) | 49 (59.8) | 317 (246–351) | <0.01 |
| Therapeutic† | 9 (11.0) | 13.9 (12.7–16.4) | 24 (29.3) | 476 (438–512) | <0.01 |
| Supratherapeutic | 6 (7.3) | 24.4 (19.5–29.4) | 9 (11.0) | 775 (646–908) | 0.25 |

*AUC/MIC, area under the curve over minimum inhibitory concentration*

* Reported p value based on the comparison of proportions between vancomycin trough–based method and AUC/MIC-based method.
† Therapeutic serum vancomycin trough concentrations defined as 15 to 20 µg/mL for severe infections and 10 to 15 µg/mL for all other conditions. Therapeutic AUC/MIC defined as 400 to 600. Concentrations/values that fall below these targets were considered subtherapeutic and those that fall above these targets were considered supratherapeutic.

To identify risk factors for subtherapeutic initial extrapolated serum vancomycin troughs and AUC/MIC, a univariate analysis was performed. A classification and regression tree (CART) analysis was used to determine the statistically significant node to classify continuous data into categorical variables, using a decision tree. Predictors included in multivariate logistic regression model were based on the univariate analysis (with a relaxed p value of <0.2 to prevent exclusion of potentially important variables), CART analyses, as well as the clinical significance of variables.[32,33] To ensure that predictors included in the multivariate logistics model were independent, multicollinearity was tested. A variance inflation factor of less than 5 would indicate that predictors were independent of one another.[34] For all other statistical analyses, a statistically significant difference was observed if p value <0.05. All statistical tests were performed with IBM SPSS Statistics 25.

## Results

**Demographics and Clinical Characteristics.** A total of 224 patients were initiated on intravenous vancomycin between January 1, 2014, and October 31, 2017. Eighty-two patients had TDM performed after the first dose of vancomycin (see Supplemental Figure S2) and were included in this study.

Of the 82 patients, 54 (65.9%) were males and 43 (52.4%) were Chinese. The median age of patients receiving vancomycin was 4.7 years (IQR, 1.2–11.8), with most being younger than 13 years (66, 80.5%). About half (40, 48.8%) of the patients had a past medical history of cancer or stem cell transplant. Of the 78 (95.1%) patients who received prior or concurrent nephrotoxic drugs, 66 (84.6%) were on piperacillin-tazobactam, and 36 (46.1%) were on aminoglycosides.

Targeted vancomycin initiation occurred in 31 of 82 patients (37.8%); 18 (58%) cultures grew coagulase-negative *Staphylococcus*, 5 (16%) grew *Streptococcus* species resistant to beta-lactams, 4 (13%) grew methicillin-resistant *Staphylococcus aureus*, and the remaining 4 (13%) grew either *Enterococcus* or *Bacillus* species.

**Primary Objective.** There was a larger proportion of target attainment when the AUC/MIC-based method (24, 29.3%) was used, compared with the trough-based method (9, 11.0%; p < 0.01) (Table 2). This suggests that 25% of dose adjustments (21 of 82 patients) could have been avoided with the AUC/MIC-based method.

**Secondary Objectives.** Univariate (Table 3) and CART analysis between patients with subtherapeutic and therapeutic initial extrapolated vancomycin troughs yielded baseline eGFR (≥52.1 mL/min/1.73 $m^2$), age (<15 years), and weight (<47.9 kg) as possible risk factors for subtherapeutic initial extrapolated vancomycin troughs. From the multivariate analysis, baseline eGFR ≥60 mL/min/1.73 $m^2$ (OR, 5.7; p = 0.04; 95% CI, 1.09–29.78) and age <13 years (OR, 6.7; p = 0.03; 95% CI, 1.24–35.97) were predictive of subtherapeutic initial extrapolated vancomycin troughs.

When using AUC/MIC as the pharmacodynamic target, age groups, baseline eGFR (≥76 mL/min/1.73 $m^2$), age (<14 years), and the indication for vancomycin were identified as significant factors for subtherapeutic AUC/MIC from the univariate (Table 3) and CART analysis. There were insufficient patients with eGFR <60 mL/min/1.73 $m^2$, hence an eGFR cutoff of 90 mL/min/1.73 $m^2$ was used in the multivariate analysis. Respiratory and central nervous system infections may be more difficult to treat; hence, these 2 indications were included as potential predictors in the multivariate analysis. The multivariate logistic regression found that age <13 years (OR, 3.4; p = 0.04; 95% CI, 1.04–11.44) increased the odds of subtherapeutic AUC/MIC.

**Clinical Outcomes.** For patients on vancomycin targeted therapy, no statistically significant differences in the incidence of treatment success, clinical success and microbial clearance, mortality, and

**Table 3.** Univariate Analysis of Factors Affecting Subtherapeutic Initial Extrapolated Vancomycin Troughs and AUC/MIC

| | Initial Extrapolated Serum Vancomycin Troughs | | | Initial Extrapolated AUC/MIC | | |
|---|---|---|---|---|---|---|
| **Risk Factors** | **Subtherapeutic (n = 67)** | **Therapeutic (n = 9)** | **p Value** | **Subtherapeutic (n = 49)** | **Therapeutic (n = 24)** | **p Value** |
| Sex, n (%) | | | 0.33 | | | 0.92 |
| Male | 41 (61.2) | 7 (77.8) | | 30 (61.2) | 15 (62.5) | |
| Female | 26 (38.8) | 2 (22.2) | | 19 (38.8) | 9 (37.5) | |
| Race, n (%) | | | 0.22 | | | 0.69 |
| Chinese | 38 (56.7) | 4 (44.4) | | 29 (59.2) | 13 (54.2) | |
| Malay | 12(17.9) | 4 (44.4) | | 8 (16.3) | 6 (25.0) | |
| Indian | 6 (9.0) | 1 (11.2) | | 5 (10.2) | 1 (4.1) | |
| Others | 11 (16.4) | 0 (0.0) | | 7 (14.3) | 4 (16.7) | |
| Age, median (IQR), yr | 4.3 (1.2–11.6) | 6.8 (1.0–15.8) | 0.48 | 4.9 (2.1–11.6) | 2.1 (0.8–14.3) | 0.52 |
| Age group, n (%) | | | 0.061* | | | 0.03* |
| <2 yr | 21 (31.3) | 4 (44.4) | | 11 (22.4) | 12 (50.0) | |
| 2 to <6 yr | 18 (26.9) | 0 (0.0) | | 17 (34.7) | 1 (4.2) | |
| 6 to <13 yr | 18 (26.9) | 1 (11.1) | | 15 (30.6) | 4 (16.7) | |
| ≥13 yr | 10 (14.9) | 4 (44.4) | | 6 (12.2) | 7 (29.2) | |
| Treatment setting, n (%) | | | 0.82 | | | 0.26 |
| Oncology | 31 (46.3) | 4 (44.4) | | 27 (55.1) | 8 (33.3) | |
| ICU | 23 (34.3) | 4 (44.4) | | 15 (30.6) | 9 (37.5) | |
| General medicine | 8 (11.9) | 1 (11.1) | | 4 (8.2) | 5 (20.8) | |
| General surgery | 5 (7.5) | 0 (0.0) | | 3 (6.1) | 2 (8.3) | |
| Weight, median (IQR), kg | 15.1 (10.0–30.0) | 22.7 (7.3–47.5) | 0.65 | 15.3 (11.4–29.9) | 14.8 (8.0–37.4) | 0.57 |
| Baseline eGFR, median (IQR), mL/min/1.73 m$^{2}$† | 95.9 (81.9–112.1) | 94.8 (60.9–99.0) | 0.19* | 96.8 (88.2–113.8) | 88.3 (70.4–102.0) | 0.04* |
| Underlying medical condition, n (%)‡ | | | 0.95 | | | 0.32 |
| Cancer/stem cell transplant | 34 (50.8) | 4 (44.4) | | 29 (69.1) | 9 (37.5) | |
| Gastrointestinal | 10 (14.9) | 3 (33.3) | | 7 (14.3) | 5 (20.8) | |
| Neurologic | 7 (10.5) | 0 (0.0) | | 3 (6.1) | 4 (16.7) | |
| Respiratory | 5 (7.5) | 1 (11.1) | | 4 (8.2) | 1 (4.2) | |
| Cardiac | 4 (6.0) | 1 (11.1) | | 3 (6.1) | 2 (8.3) | |
| Endocrine/renal | 4 (6.0) | 1 (11.1) | | 2 (4.1) | 2 (8.3) | |
| None | 11 (16.4) | 2 (22.2) | | 9 (18.4) | 3 (12.5) | |
| Others | 1 (1.5) | 0 (0.0) | | 0 (0.0) | 1 (4.2) | |
| Concurrent or prior nephrotoxic agents, n (%) | 63 (94.0) | 9 (100) | 0.45 | 47 (95.9) | 22 (91.7) | 0.45 |
| Indication of vancomycin by site of infection, n (%) | | | 0.92 | | | 0.18* |
| Blood or line | 41 (61.2) | 6 (66.7) | | 33 (67.4) | 14 (58.4) | |
| Central nervous system | 11 (16.4) | 1 (11.1) | | 5 (10.2) | 6 (25.0) | |
| Respiratory | 10 (14.9) | 1 (11.1) | | 8 (16.3) | 2 (8.3) | |
| Skin, soft tissues, bone and joint | 3 (4.5) | 1 (11.1) | | 1 (2.0) | 2 (8.3) | |
| Others | 2 (3.0) | 0 (0.0) | | 2 (4.1) | 0 (0.0) | |

*AUC/MIC, area under the curve over minimum inhibitory concentration; eGFR, estimated glomerular filtration rate; ICU, intensive care unit*

* Risk factors included in the multivariate logistic analysis.
† eGFR based on the modified Schwartz equation.[15]
‡ Patients may have more than 1 underlying medical condition.

nephrotoxicity were observed when comparing non-therapeutic against therapeutic vancomycin troughs or AUC/MICs ($p > 0.05$; Table 4).

**Vancomycin Dosing.** Based on the mean vancomycin dose per day calculated for each subgroup of patients, vancomycin trough targets would require that larger

**Table 4.** Clinical Outcomes Based on Either Extrapolated Vancomycin Trough or AUC/MIC Method Among Groups

| | Subtherapeutic | Therapeutic | Supratherapeutic | p Value |
|---|---|---|---|---|
| No. of vancomycin courses, n (%)* | | | | |
| Based on serum vancomycin troughs | 23 (74.2) | 6 (19.3) | 2 (6.5) | |
| Based on AUC/MIC | 17 (54.8) | 10 (32.3) | 4 (12.9) | |
| Incidence of treatment success, n (%)†‡ | | | | |
| Based on serum vancomycin troughs | 16 (70.0) | 6 (100.0) | 1 (50.0) | 0.23 |
| Based on AUC/MIC | 12 (70.6) | 8 (80.0) | 3 (75.0) | 0.86 |
| Incidence of clinical success, n (%)† | | | | |
| Based on serum vancomycin troughs | 18 (78.3) | 6 (100.0) | 1 (50.0) | 0.26 |
| Based on AUC/MIC | 14 (82.3) | 8 (80.0) | 3 (75.0) | 0.94 |
| Incidence of microbial clearance, n (%)† | | | | |
| Based on serum vancomycin troughs | 23 (100.0) | 6 (100.0) | 2 (100.0) | 0.65 |
| Based on AUC/MIC | 17 (100.0) | 10 (100.0) | 4 (100.0) | 0.97 |
| 30-day all-cause in-hospital mortality, n (%)† | | | | |
| Based on serum vancomycin troughs | 1 (4.3) | 0 (0.0) | 0 (0.0) | 0.84 |
| Based on AUC/MIC | 1 (5.9) | 0 (0.0) | 0 (0.0) | 0.65 |
| Incidence of nephrotoxicity, n (%)† | | | | |
| Based on serum vancomycin troughs | 3 (13.0) | 1 (16.7) | 0 (0.0) | 0.83 |
| Based on AUC/MIC | 3 (17.6) | 0 (0.0) | 1 (25.0) | 0.31 |

*AUC/MIC, area under the curve over minimum inhibitory concentration*

* Percentage based on total number of patients on targeted vancomycin therapy.
† Percentage based on total number of patients in each subgroup (subtherapeutic, therapeutic, supratherapeutic) according to either the trough or AUC/MIC method.
‡ Treatment success is a composite outcome of clinical success, microbial eradiation, and lack of 30-day mortality.

**Table 5.** Mean Pharmacokinetic Variables and Mean Adjusted Initial Dose by Age and Baseline eGFR Categories

| | Half-life, hr | | Clearance, L/kg hr | | Volume of Distribution, L/kg | | Mean Vancomycin Dose per Day (mg/kg/day) Based on | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Therapeutic Vancomycin Trough | AUC/MIC = 400 | AUC/MIC = 500 | AUC/MIC = 600 |
| Age | | | | | | | | | | |
| <13 yr | 2.61 | 0.84 | 0.18 | 0.08 | 0.62 | 0.16 | 99.89 ± 32.51 | 73.01 ± 32.55 | 91.27 ± 40.69 | 109.52 ± 48.83 |
| ≥13 yr | 3.01 | 0.77 | 0.12 | 0.04 | 0.49 | 0.09 | 71.49 ± 25.08 | 48.14 ± 14.20 | 60.17 ± 17.73 | 72.21 ± 21.28 |
| Baseline eGFR | | | | | | | | | | |
| <60 mL/min/1.73 $m^2$ | 2.90 | 0.91 | 0.16 | 0.09 | 0.59 | 0.17 | 88.29 ± 35.41 | 64.05 ± 35.39 | 80.07 ± 44.24 | 96.08 ± 53.09 |
| ≥60 mL/min/1.73 $m^2$ | 2.27 | 0.45 | 0.19 | 0.05 | 0.61 | 0.13 | 106.77 ± 24.06 | 76.71 ± 19.96 | 95.89 ± 24.94 | 115.07 ± 29.93 |

*AUC/MIC, area under the curve over minimum inhibitory concentration; eGFR, estimated glomerular filtration rate*

vancomycin doses be given to patients, compared with AUC/MIC targets of 400 to 600. From Table 5, using an AUC/MIC of 400, initial empiric vancomycin doses can remain at 60 to 70 mg/kg/day for all patients. However, empiric doses may increase to 80 to 100 mg/kg/day if patients have high vancomycin clearance or require a larger dose for difficult-to-treat infections.

## Discussion

This study found that AUC/MIC-based vancomycin TDM improved therapeutic target attainment when intravenous vancomycin was initiated at 60 mg/kg/day. Patients with age <13 years had an increased risk of subtherapeutic initial serum vancomycin troughs and AUC/MIC, whereas patients with eGFR ≥60 mL/min/1.73 $m^2$

had an increased risk of subtherapeutic initial vancomycin troughs. However, an initial empiric dose of intravenous vancomycin 60 to 70 mg/kg/day remained adequate (Table 5) if an AUC/MIC target of 400 was used. There were no differences in clinical outcomes and nephrotoxicity among patients with subtherapeutic, therapeutic, and supratherapeutic targets regardless of the TDM method used.

Given the larger proportion of therapeutic attainment with AUC/MIC targets compared with serum troughs, this suggests that the AUC/MIC-based TDM method would minimize the need for dose adjustments. In this study, 25% of dose adjustments could have been avoided if the AUC/MIC-based method had been used instead of the trough-based method, though rates of nephrotoxicity remain similar among groups. This may be explained by the findings of Le et al,[35] who found that AUC/MIC of 400 correlates to serum vancomycin trough concentrations of approximately 8 to 9 µg/mL. Hence, AUC/MIC monitoring might be the preferred monitoring method to reduce excessive vancomycin doses that may contribute to nephrotoxicity, reduce need for multiple dose adjustments, yet ensuring vancomycin's efficacy.[27,36]

This study has identified age <13 years and eGFR ≥60 mL/min/1.73 $m^2$ as risk factors for subtherapeutic vancomycin serum troughs. Buckel et al[43] also reported baseline eGFR (OR, 1.17; 95% CI, 1.01–1.36) and age <12 years (OR, 3.06; 95% CI, 1.03–9.10; p = 0.05) as risk factors for subtherapeutic vancomycin troughs <10 µg/mL. However, Buckel et al[43] did not assess the relationship between pediatric patients with nontherapeutic vancomycin troughs and their clinical outcomes, making it difficult to justify the need for more aggressive empiric doses. Pediatric patients <13 years have a potentially higher eGFR than adults, explaining the increased clearance of vancomycin.[37] In this study, oncology patients were not at risk for subtherapeutic vancomycin targets probably owing to small numbers. However, in literature, cancer-induced vancomycin clearance rates may be increased by 50% to 75% as compared with non-oncology patients.[10,38,39] To date, no other study has been published looking into risk factors for subtherapeutic AUC/MIC.

No difference in clinical outcomes between subtherapeutic, therapeutic, and supratherapeutic groups, regardless of TDM method, was reported in this study. This could be attributed to a small number of patients with MRSA infections, which the AUC/MIC and trough targets were derived from. Few pediatric studies, with conflicting findings, have been done to evaluate the correlation of vancomycin troughs with clinical outcomes. A retrospective review of pediatric intensive care unit patients found that lower serum vancomycin troughs were associated with increased mortality.[40] However, a study by Yoo et al[8] found no statistically significant difference in 30-day mortality and recurrent bacteremia between patients with initial serum vancomycin trough concentrations of <10 µg/mL and ≥10 µg/mL (p = 0.899 and p = 0.754 respectively), but was associated with prolonged bacteremia. For AUC/MIC-based monitoring, clinical outcomes in pediatric patients have not been well evaluated. However, AUC/MIC targets of less than 400 have been associated with an increased risk of vancomycin treatment failure in adult patients with MRSA bacteremia, and an increased 30-day mortality in adult patients with enterococcal bacteremia.[28,41] More prospective studies need be done to justify the correlation of clinical outcomes to vancomycin targets in pediatric patients, particularly in non-MRSA infections.[42] This would especially benefit settings where vancomycin AUC/MIC TDM requires additional funding and training.

In this study, an exploratory analysis looking at empiric doses required to achieve therapeutic vancomycin targets was done. When the trough-based method is used, median vancomycin doses of up to 100 mg/kg/day may be required for patients <13 years or with eGFR ≥60 mL/min/1.73 $m^2$. However, using the AUC/MIC-based method, smaller median vancomycin doses of 60 to 70 mg/kg/day could achieve AUC/MIC targets. All patients in this study had half-lives and volumes of distribution (Table 5) similar to pediatric vancomycin population kinetics, supporting the credibility of this proposed dosing.[10] In the latest vancomycin consensus guidelines, empiric vancomycin doses of 60 to 80 mg/kg/day were recommended for pediatric patients 3 months to 12 years of age.[1] Hence, to reduce the risk of nephrotoxicity, more aggressive initial doses might not be necessary with AUC/MIC-based monitoring.

Some other strategies have been proposed to optimize and reduce time taken to achieve therapeutic targets. These include the use of population kinetic models specific to an institution or geographic area; Bayesian models, which can also reduce the need for multiple blood draws; and administration of a loading dose.[6,16,21,43] Use of lower serum vancomycin trough concentration targets of 10 to 15 may also be considered if AUC/MIC-based monitoring is not available.[35] More well-designed, prospective studies will be required to provide evidence for these practices, to optimize vancomycin therapy in pediatric patients.

While there are other studies correlating vancomycin AUC/MICs with corresponding trough concentrations, this was the first study assessing risk factors for subtherapeutic AUC/MIC. This study also attempted to associate target attainment to clinical outcomes. This is highly relevant to practice because the latest vancomycin guidelines recommend that AUC/MIC monitoring be done within 24 to 48 hours of initiating therapy.[1] Hence, this study justifies the use of vancomycin AUC/MIC monitoring to reduce unnecessarily large vancomycin

doses and to reduce the need for dose adjustments, in an attempt to improve clinical outcomes.

Limitations of this study include the following: 1) This is a retrospective, single center study with a small sample size; 2) The definition of stable renal function was assumed from stable eGFR and no documented history of renal disease. Although this assumption may potentially introduce bias, it may not be unreasonable given that most patients in our population do not have renal dysfunction, and clear documentation would be provided if there were; 3) The initial serum vancomycin trough concentrations and AUC/MIC were extrapolated from vancomycin concentrations obtained after the first dose of vancomycin. However, this extrapolation was done by using a commercially available pharmacokinetics software based on validated one-compartmental pharmacokinetic equations in pediatric patients[19,20]; 4) The empiric vancomycin doses proposed, based on age and baseline eGFR, were determined by using initial vancomycin dose adjustments but did not consider the cumulative effect of vancomycin; 5) Target AUC/MIC ratios from the guidelines were extrapolated from studies in patients with severe MRSA infections.[1] However in this study, most targeted vancomycin therapy was initiated for non-MRSA infections and MIC data were assumed to be 1 µg/mL, based on epidemiologic studies. Thus, more studies are required to determine suitable vancomycin therapeutic targets for non-MRSA infections.

## Conclusion

AUC/MIC-based vancomycin TDM improved therapeutic target attainment when compared with the trough-based method with 60 mg/kg/day of intravenous vancomycin. Baseline eGFR ≥60 mL/min/1.73 $m^2$ and age <13 years were identified as risk factors for initial subtherapeutic vancomycin targets. No difference in clinical outcomes were detected between therapeutic and nontherapeutic targets regardless of the monitoring method used, likely owing to the small sample size. Hence, this study supports the shift towards vancomycin AUC/MIC-based monitoring in pediatric patients to reduce the need for dose adjustments and excessively large vancomycin doses. Future prospective studies with larger sample size will be required to determine the optimal vancomycin dose or strategy for maximal efficacy and safety.

## Article Information

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