CLINICAL INVESTIGATION

Vancomycin Dosing and Pharmacokinetics in Postoperative Pediatric Cardiothoracic Surgery Patients

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OBJECTIVES: This study compared vancomycin trough concentrations and pharmacokinetic parameters in pediatric cardiothoracic surgery (CTS) patients versus those in controls receiving 20 mg/kg/dose, intravenously, every 8 hours.

METHODS: A retrospective study was conducted in children <18 years of age, following CTS, versus an age- and sex-matched control group. The primary objective was to determine differences in trough concentrations between groups. Secondary objectives included comparisons of pharmacokinetics between groups and development of vancomycin-associated acute kidney injury (AKI), defined as a doubling in serum creatinine from baseline. Also dosing projections were developed to target an area-under-the-curve-to-minimum inhibitory concentration (AUC:MIC) ratio of ≥ 400 .

RESULTS: Twenty-seven patients in each group were evaluated. Mean trough concentrations were significantly different between groups (CTS: 18.4 mg/L; control: 8.8 mg/L; $p < 0.01$). Vancomycin-associated acute kidney injury AKI was significantly higher in the CTS group than in controls (25.9% versus 0%, respectively, $p < 0.01$). There were significant differences in vancomycin elimination rates, with a high degree of variability, but no statistical differences in other parameters. Based on dosing projections, CTS patients would require 21 to 88 mg/kg/day, with a dosage interval determined by the child's glomerular filtration rate to achieve the target AUC:MIC ≥ 400 .

CONCLUSIONS: Vancomycin dosage of 20 mg/kg/dose intravenously every 8 hours achieved significantly higher trough concentrations in CTS patients than in controls. Pharmacokinetic parameters were highly variable in CTS patients, indicating more individualization of dosage is needed. A future prospective study is needed to determine whether the revised dosage projections achieve the AUC:MIC target and to determine whether these regimens are associated with less vancomycin-associated AKI.

INDEX TERMS: cardiothoracic surgery, pediatrics, pharmacokinetics, vancomycin

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INTRODUCTION

Vancomycin remains the mainstay of therapy for most severe methicillin-resistant *Staphylococcus aureus* (MRSA) infections based on guidelines from the Infectious Diseases Society of America (IDSA) in pediatric and adult patients alike.¹ IDSA recommends a dosage of 60 mg/kg/day, targeting trough concentrations of at least 10 mg/L and 15 to 20 mg/L to treat deep-seated infections, including bacteremia, osteomyelitis, meningitis, infective endocarditis, pneumonia,

and severe skin and soft tissue infections in pediatric patients, despite limited data.^{1,2} These trough concentrations are suggested surrogates for achieving an area under the curve-to-minimum inhibitory concentration (AUC:MIC) target ratio of ≥ 400 in adult patients, which is the accepted pharmacodynamic target for serious infections caused by MRSA.^{1–3} Clinical outcome data regarding the AUC:MIC target goal in pediatric patients are currently unavailable, thus adult goals are extrapolated to infants and children. More recently, pharmacokinetic modeling

has suggested that lower trough concentrations may be sufficient to achieve an AUC:MIC ≥ 400 in pediatric patients.⁴

Vancomycin is used for antibiotic prophylaxis in children undergoing cardiothoracic surgery (CTS) for children with congenital heart disease who have an allergy to beta-lactam agents, a history of MRSA infection, and for those with delayed sternal closure.⁵⁻⁸ In children with congenital heart disease, Marlowe et al⁵ noted that lower vancomycin doses are required to reach target trough concentrations than in otherwise healthy patients; however, AUC targets have not been investigated. During and after palliative surgery for heart defects, there are many risk factors that may further decrease the dosing requirements for vancomycin because of reduced renal clearance, including cardiopulmonary bypass (CPB), use of vasoactive agents, and use of concomitant nephrotoxic medications.^{5,6} All of these factors could potentially decrease vancomycin clearance and increase risk for acute kidney injury (AKI). Based on the published evidence for targeting higher trough concentrations for vancomycin in adult patients, a vancomycin dosage protocol was adopted prior to collection of these data in a pediatric tertiary care medical center. With known differences in pharmacokinetic parameters in CTS patients, it was not clear whether protocol dosages achieved goal serum concentrations without increasing the risk of AKI compared to those in other pediatric patients. The primary goal of this study was to compare the resultant vancomycin trough concentrations in postoperative CTS patients versus those in non-CTS patients by using a vancomycin dosage protocol. Secondly, this study assessed factors that may alter the clearance of vancomycin and the likelihood of AUC:MIC target ≥ 400 .

METHODS

Study Design

This retrospective, cohort, Institutional Review Board-approved study was conducted at a tertiary care, academic medical center licensed for 230 beds, including 25 pediatric intensive care unit (PICU) beds. Based on physicians' records, approximately 200 children annually underwent CTS at this academic medical center in the 2 years prior to the study, of which an estimated one-fourth were empirically treated

with vancomycin postoperatively primarily due to open sternum following surgery. In the fall of 2008, an intravenous (IV) vancomycin protocol was developed at this institution. The protocol recommended a starting dosage of 60 mg/kg/day, divided every 8 hours, for all pediatric patients (excluding premature neonates) to achieve a target trough concentration of 10 to 20 mg/L, depending on clinical indication. Patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² standardized were excluded from the protocol. As part of the protocol, trough concentrations were obtained prior to the third dose.

Children in the study group were included if they underwent CTS and received IV vancomycin by protocol within 24 hours after surgery from September 1, 2008, through August 31, 2009. An age- and sex-matched cohort admitted during the study period who received IV vancomycin by protocol and who did not undergo CTS was included as the control group. Patients were identified using electronic medical records (EMR; Meditech database (Medical Information Technology, Inc.; Westwood, MA). Patients were excluded if they did not have at least one appropriately drawn vancomycin concentration (i.e., within 1 hour of the end of the 8-hour dosage interval following at least 3 doses). For the study group, only vancomycin concentrations following CTS were included.

Study Objectives and Data Collection

The EMR was used as the primary source for data collection; physicians' progress and nurses' notes from paper charts were used to obtain data not found in the EMR. Baseline demographic data including sex, height, weight, and age at the time of surgery were collected for all patients. Initial vancomycin dose and dosage interval were recorded, as well as all serum concentrations obtained. The first appropriately drawn trough concentration was used for the primary outcome. Timing of dosage in relation to serum concentrations was also recorded. Laboratory data including serum creatinine (SCr) and urine output (UOP) (mL/kg/hr) were collected to assess renal function at baseline and throughout the duration of vancomycin therapy.

All potentially nephrotoxic medications used concomitantly with vancomycin were recorded in order to assess other risk factors for reduced

vancomycin clearance. Additionally, data were collected from each patient's surgical procedure to assess factors that might have affected renal perfusion and thus vancomycin clearance. These data included type of cardiac surgery, duration of the procedure, use of CPB, duration of CPB, and concomitant vasopressors or inotropes during and after surgery. Patients receiving postoperative extracorporeal membrane oxygenation (ECMO) were also identified.

The primary objective of the study was to compare differences in vancomycin trough concentrations between groups. There were several secondary objectives that were also assessed. First, there was a comparison of the percentage of patients who developed AKI between groups. For this study, vancomycin-associated AKI was defined as a doubling in SCr during vancomycin from baseline.⁹ The eGFR was estimated using the modified Schwartz equation for each patient and was compared between groups.¹⁰ In addition, there was a comparison of the percentage of patients taking nephrotoxic medications. Finally, vancomycin pharmacokinetics were compared between groups. Projected dosage recommendations were calculated to achieve target AUC:MIC ratio values of ≥ 400 .

Pharmacokinetic Analysis

Vancomycin pharmacokinetics were fitted using Pmetrics software (Laboratory of Applied Pharmacokinetics and Bioinformatics, Children's Hospital of Los Angeles; Los Angeles, CA) for each patient, each study group, and both study groups combined.¹¹ Pharmacokinetic parameters of elimination rate fitted for the Pmetrics software (K_{el}) and volume of distribution in L/kg fitted for the Pmetrics program (V_d) were fitted to a 1-compartment intermittent infusion model based on timing of dose and serum vancomycin concentrations. Prior studies using this model reported that the best covariates are age, weight, and creatinine clearance.¹² Subject age, weight (in kg), and creatinine clearance (eGFR in mL/min/1.73 m²) were used as covariates. All subjects had at least one serum vancomycin concentration included in the pharmacokinetic analysis. All serum vancomycin concentrations that were < 5 mg/L were excluded from pharmacokinetic analysis, as the concentrations were considered nondetectable.

Vancomycin serum concentrations were mea-

sured using a Beckman Coulter model DxC800 system (Beckman Coulter, Brea, CA), using a particle-enhanced turbidimetric inhibition immunoassay method with coefficients of variation ranging from 2.29% to 4.01%. An assay coefficient of variation of 5% was used for the error portion of the model. Vancomycin elimination rate (K_{el}) equaled $[K_{el} \times eGFR]$ and volume of distribution (VD) equaled $[V_d \times \text{subject weight}]$. Vancomycin clearance (CL) was determined by multiplying $[K_{el} \times VD]$. AUC for 24 hours was determined for CTS patients by using the total dose for the first 24 hours divided by CL. AUC:MIC values were determined using MIC values of 0.5, 1.0, and 2.0 mg/L. Projected dosages and resultant concentrations were calculated using the equations of Sawchuk and Zaske.¹³

Statistical Methods

Comparison of vancomycin trough concentrations and pharmacokinetic parameters was assessed using unequal variance t-test. Nominal data were assessed using the Chi-square test. Continuous data were analyzed via a two-tailed Student *t* test. Data management was performed using SAS version 9.2 software (SAS, Cary, NC), with the a priori alpha set at a p value of < 0.05 .

RESULTS

Forty-four patients received vancomycin following CTS. Four patients were excluded due to inappropriately obtained trough concentrations, and 13 were excluded due to nonprotocol dosage regimens. This left 27 patients available for evaluation of primary and secondary outcomes (Table 1). Eleven patients (40.7%) had single-ventricle anatomy. Twenty-three patients (88.9%) were placed on CPB during surgery for a mean 154 minutes. Six children (22.2%) were placed on ECMO following surgery. A median of three postoperative inotropes were infused per CTS patient; the most common inotropes were milrinone in 85.2% and dopamine in 81.5% of CTS patients.

Twenty-seven patients were included in the control group for the primary outcome and 26 for pharmacokinetic fitting (1 subject had an undetectable concentration and was not included). Males represented 55.6% of patients in each group. Mean age was 1.1 ± 1.5 years in both groups. There were no significant differences

Table 1. Patient Baseline Demographic and Renal Function Data

Variable	CTS Group (n = 27)	Controls (n = 27)	p Value
	N (%) or Mean $\pm$ SD		
Age (yr)	1.1 $\pm$ 1.5	1.1 $\pm$ 1.5	NS
Males	15 (55.6)	15 (55.6)	NS
Weight (kg)	7.8 $\pm$ 4.7	8.2 $\pm$ 5.0	NS
Height (cm)	67.0 $\pm$ 16	67.8 $\pm$ 19	NS
Baseline SCr	0.3 $\pm$ 0.2	0.3 $\pm$ 0.1	NS
Baseline eGFR (mL/min/1.73 m ²)	109 $\pm$ 40	113 $\pm$ 52	NS
Minimum eGFR (mL/min/1.73 m ²)	55 $\pm$ 6	101 $\pm$ 9	<0.01
Maximum increase in SCr during therapy (mg/dL)	0.4 $\pm$ 0.5	0.02 $\pm$ 0.04	<0.01
Patients with doubling in SCr from baseline	7 (25.9)	0	<0.01
Average UOP during therapy (mL/kg/h)	3.9 $\pm$ 1.2	4.2 $\pm$ 1.6	NS
Patients with $\geq$ 1 potentially nephrotoxic medication	25 (92.6)	7 (25.9)	<0.01

CTS, cardiothoracic surgery; eGFR, estimated glomerular filtration rate determine by the Schwartz equation⁶; NS, not statistically significant; SCr, serum creatinine; UOP, urine output

between groups in the baseline variables (Table 1). The indications for vancomycin therapy in the control group were skin and soft tissue infections (n = 9), suspected respiratory illness (n = 6), and suspected sepsis (n = 12).

For the primary outcome, mean trough concentrations were significantly different between groups (CTS: subjects: 18.4 $\pm$ 6.0 mg/L; control: 8.8 $\pm$ 6.0 mg/L; $t = 4.4$, $p < 0.01$) (Table 2). Fourteen patients (51.9%) in the CTS and 10 (37%) in the control groups had trough concentrations between 10 and 20 mg/L. There were significant differences between the number of patients with troughs >20 mg/L in the CTS group and in the control group, 9 (range: 22.9–40 mg/L) versus 1 (23 mg/L), $p < 0.01$. Of the patients with supra-therapeutic troughs, only 6 of the CTS patients had a decrease of $>50\%$ in eGFR. The mean duration of vancomycin therapy was 6.0 days in the CTS group and 7.5 days in the control group. Additional information regarding vancomycin regimens and concentrations can be found in Table 2.

In secondary analyses, mean baseline SCr values were similar between groups (Table 1). During vancomycin therapy, the percentage of patients with vancomycin-associated AKI was significantly greater in the CTS group versus than in controls, 25.9% versus 0%, respectively ($p < 0.01$). A significantly higher proportion of patients in the CTS group received at least one potentially nephrotoxic medication (93% in the

CTS group vs. 26% in the control group, $p < 0.01$), the majority of which were loop diuretics. Excluding loop diuretics, there were two patients in each group who received a potentially nephrotoxic medication (i.e., aminoglycosides and nonsteroidal anti-inflammatory drugs).

Table 3 includes mean pharmacokinetic parameters derived by Pmetrics, calculated pharmacokinetic parameters, and resultant 24-hour AUC:MIC ratios. Statistically significant differences were found between Ke_0 and Ke_1 values. No statistically significant differences were found in V_d , V_d , or CL, but high variability was noted in these values. Projected vancomycin doses for CTS patients with dosing intervals based on eGFR values of 30, 60, 90, and 120 mL/min/1.73 m² with resultant AUC:MIC values are listed in Table 4. Based on these calculations, the projected dosage regimens would be approximately 21 to 88 mg/kg/day in divided doses. It is important to note that none of these projections would achieve a target AUC:MIC ≥ 400 with a projected MIC of 2 mg/L.

DISCUSSION

This is one of a few studies that have evaluated vancomycin dosages and pharmacokinetics in postoperative CTS children. To our knowledge, only three studies have investigated the pharmacokinetics and dosages of vancomycin in children with congenital heart disease and status

Table 2. Vancomycin Regimen and Concentrations

Variable	CTS Group (n = 27) N (%) or Mean $\pm$ SD	Controls (n = 27) N (%) or Mean $\pm$ SD	p Value
Initial dose			
mg/kg/dose	19.8 $\pm$ 1.0	20.0 $\pm$ 0.42	NS
mg/dose	154.2 $\pm$ 94.1	162.3 $\pm$ 97.1	NS
Duration (days)	6.0 $\pm$ 3.1	7.5 $\pm$ 8.2	NS
Serum trough concentrations (mg/L)			
Mean $\pm$ SD	18.4 $\pm$ 6.0	8.8 $\pm$ 6.0	<0.01
Number between 10 and 14	10 (37.0)	7 (25.9)	NS
Number between 15 and 20	4 (14.8)	3 (11.1)	NS
Number <10 mg/L	4 (14.8)	16 (59.3)	<0.01
Number >20 mg/L	9 (33.3)	1 (3.7)	<0.01

CTS, cardiothoracic surgery; NS, not statistically significant

post-CTS.⁵⁻⁷ In our study, we noted significant differences in mean trough concentrations in CTS children versus those in controls, suggesting that these children exhibited decreased vancomycin CL. Children undergoing CTS surgery have many factors, including low cardiac output state and CPB, that may increase the likelihood of AKI and altered vancomycin pharmacokinetics.⁵⁻⁶ Marlowe et al.⁵ described the pharmacokinetics of vancomycin in 36 children with congenital heart disease. They found that the average elimination half-life of vancomycin in these patients was 5.94 hours with a $K_{el} = 0.1167 \text{ hr}^{-1}$. We found a similar half-life and K_{el} in our CTS patients, 6.5 hours and 0.1062 hr^{-1} , respectively (Table 3). In contrast, our controls had a shorter half-life of 3.5 hours with a faster K_{el} (0.1996 hr^{-1}), which is comparable to values in previously published reports in healthy infants and children.^{12,14}

Based on the decreased vancomycin clearance in this population, Marlowe et al.⁵ suggested that children with congenital heart disease receive a longer dosage interval than otherwise healthy children and recommended a dosage of 10 mg/kg/dose every 12 hours. However, it should be noted that that study was targeting vancomycin peak and trough concentrations of 20 to 40 mg/L and 5 to 10 mg/L, respectively. Based on new recommendations from IDSA in children and adults, dosage recommendations of Marlowe et al.⁵ would not target the trough goal concentrations of 10 to 20 mg/L and would therefore not achieve the desired AUC:MIC target of ≥ 400 .¹²

Our study is the first to describe dosage recom-

mendations to achieve AUC:MIC targets for MIC values of 0.5, 1.0, and 2.0 mg/L in children who have undergone CTS. In this study, we used pharmacokinetic parameters to determine projected vancomycin doses based on eGFR. Previous studies have used pharmacokinetic modeling to determine dosage recommendations to achieve a target AUC:MIC ≥ 400 , but those studies did not explicitly study the dosage requirements in children undergoing CTS.^{4,15,16} Based on our analysis, we determined that CTS patients would require approximately 21 to 88 mg/kg/day with a dosage interval as determined by the child's eGFR to achieve an AUC:MIC ≥ 400 for MICs of 0.5 and 1 mg/L (Table 4). However, none of these dosing regimens was able to achieve this target with MICs of 2 mg/L. This dosage regimen is in contrast to requirements from two recent studies of non-CTS infants and children of 60 to 70 mg/kg/day in divided doses.^{4,15}

It should be noted that these studies did not explicitly study children with renal insufficiency. Recently, Le et al.¹⁶ evaluated the pharmacokinetics in 63 children with renal insufficiency (defined as $\text{SCr} > 0.9 \text{ mg/dL}$) compared with 63 children in an age- and weight-matched control group. They used Monte Carlo simulation and recommended a dosage regimen of 45 mg/kg/day divided every 8 hours to achieve an AUC:MIC ≥ 400 . It is difficult to compare our findings with those of Le et al.¹⁶ because they included only infants ≥ 3 months of age, and we included a number of infants < 3 months of age in the CTS group. In addition, they did not specify admission diagnoses,

Table 3. Derived Pharmacokinetic Parameters from Individual Fitting

Parameter	CTS Group (n = 27) (mean ± SD)	CTS Group 95% CI	Controls (n = 26)* (mean ± SD)	Controls 95% CI	p-Value
Ke_0 (hr ⁻¹)	0.0011 ± 0.0007	0.0008 to 0.0014	0.0022 ± 0.0011	0.0017 to 0.0028	< 0.01
Kel (hr ⁻¹)	0.1062 ± 0.0568	0.0802 to 0.1321	0.1996 ± 0.0906	0.1573 to 0.2402	< 0.01
V_0 (L/kg)	1.2 ± 0.8	0.9 to 1.6	0.9 ± 0.6	0.6 to 1.2	NS
VD (L)	9.5 ± 7.7	6.0 to 13.1	8.7 ± 8.0	4.9 to 12.5	NS
CL (L/hr)	0.7 ± 0.5	0.5 to 0.9	1.1 ± 0.8	0.7 to 1.5	NS
24 hr dose (mg)	395 ± 231	289 to 501	493 ± 230	395 to 601	NS
AUC ₂₄ (in mg/L*hr) ^j	726.6 ± 254.5	610.0 to 843.1	835.1 ± 535.3	584.8 to 1085.5	NS
AUC:MIC _{0.5} ratio	1453.1 ± 509.0	1220.1 to 1686.2	1670.3 ± 1070.7	1169.6 to 2171.0	NS
AUC:MIC _{1.0} ratio	726.6 ± 254.5	610.0 to 843.1	835.1 ± 535.3	584.8 to 1085.5	NS
AUC:MIC _{2.0} ratio	363.3 ± 127.3	305.0 to 421.5	417.6 ± 267.7	292.4 to 542.7	NS

AUC, Area-under-the-curve; CI, 95% confidence interval (two-tailed, $p=0.025$); CL, clearance; CTS, cardiothoracic surgery; Ke_0 , elimination rate fitted for the Pmetrics program; Kel , elimination rate; MIC, minimum inhibitory concentration; NS, not statistically significant; V_0 , volume of distribution in L/kg fitted for the Pmetrics program; VD, volume of distribution in liters.

* One patient in the control group was excluded due to an undetectable trough concentration.

so it is not clear if they included any patients with CTS. Based on these factors, it is difficult to interpret these results given that children status post-CTS have altered vancomycin pharmacokinetic parameters.

Our pharmacokinetic analysis did not demonstrate significant differences in V_0 , VD, or vancomycin CL; however, the variance seen in these two values underscores the need to individualize drug therapy by using pharmacokinetic models.¹⁷ Our study data suggest that obtaining an AUC:MIC ≥ 400 using intermittent dosage would be very difficult with MIC values >1 mg/L or in patients with high eGFR rates. Pai et al¹⁷ suggested that the variability in vancomycin pharmacokinetics makes using a single trough concentration as a surrogate marker for AUC difficult; however, this is commonly done in clinical practice. Calculating individualized AUC estimates would be much more accurate, especially in children as diverse as those requiring CTS. AUC values greater than 1300 mg*hr/L pose a 2.5-fold increased risk of probable vancomycin-associated AKI.¹⁸ Thus, vancomycin has a relatively narrow AUC response range of 400 to possibly 700 to 1300 mg*hr/L.¹⁷ It is the opinion of the present authors that this narrow AUC range supports individualization of vancomycin by AUC:MIC calculations rather than dosage adjustments by linear extrapolation of trough concentrations.

In our study, we noted that 25% of children

post-CTS versus 0% of controls developed vancomycin-associated AKI. Three recent studies evaluated vancomycin-associated AKI in critically ill children.^{6,19,20} In these studies, investigators observed vancomycin-associated AKI occurred in 5.4% to 17.2% of patients. It is difficult to compare these studies given the different definitions of AKI that were used. Cies and Shankar¹⁹ defined vancomycin-associated AKI as an absolute increase in SCr of 0.3 mg/dL or a 50% increase in SCr from baseline, documented on two separate occasions at least 24 hours apart. Totapally et al²⁰ defined it as 50% decrease in eGFR from baseline according to pediatric risk, injury, failure, loss, and end-stage renal disease (pRIFLE) criteria.^{9,21} It should be noted that both of these studies included critically ill children receiving vancomycin who were admitted for both medical and surgical diagnoses.

Currently, there is not a well-accepted definition of AKI in children undergoing CTS. We used a definition similar to that of Moffett et al⁶, where we defined vancomycin-associated AKI as a doubling in SCr from baseline. Moffett et al⁶ conducted a retrospective study including 120 children in the cardiac ICU and found the overall incidence of vancomycin-induced AKI was 7.2%. Our study included a higher percentage of children requiring ECMO, who developed AKI than their study (22.2% versus 13.3%). Moffett et al⁶ found that exposure to ECMO was independently associated with development of

Table 4. Dosage and AUC:MIC Projections in CTS Patients Based on Renal Function

eGFR	Ke	VD (L/kg)	Dosing Interval*	Rounded Dosing Interval†	Dose (mg/kg)	24-hr Dose (mg/kg)	AUC24	AUC: MIC _{0.5ratio}	AUC: MIC _{1.0ratio}	AUC: MIC _{2.0ratio}
30	0.0350	1.2	20.8	24	21	21	495.5	991.0	495.5	247.7
60	0.0701	1.2	10.9	12	22	44	504.2	1008.3	504.2	252.1
90	0.1051	1.2	7.6	8	22	66	512.9	1025.9	512.9	256.5
120	0.1402	1.2	5.9	6	22	88	521.8	1043.6	521.8	260.9

AUC, area-under-the-curve; AUC:MIC, area-under-the-cure divided by the minimum inhibitory concentration; eGFR, glomerular filtration based on the Schwartz equation ($\text{mL/min}/1.73\text{m}^2$);

Ke, elimination rate; VD, volume of distribution.

* Projected dosing interval based on mathematical calculations;

† Dosing interval rounded to standard administration times; dose rounded to nearest whole number; rounded to nearest whole number.

vancomycin-associated AKI (odds ratio: 14.4; 95% confidence interval: 1.02-203, $p = 0.048$). In addition, we had a significantly higher percentage of children with single ventricles who underwent surgical repair than Moffett et al⁶ did (40.7% vs. 11.7%, respectively). It is reasonable to assume that both of these factors contributed to the higher percentage of vancomycin-associated AKI in our study.

Our study has limitations that must be addressed. First, due to the retrospective nature of the study, we were unable to control for specific variations in monitoring and dosage changes. Dosage adjustments were made by prescribers, and standard dosage adjustments were not part of the protocol. In the present study, we attempted to calculate eGFR based on the modified Schwartz equation.¹⁰ Currently, all laboratories use isotope dilution mass spectrometry (IDMS) to assess SCr. Using the IDMS approach, studies have shown that the modified Schwartz equation can overestimate eGFR by 20% to 40%. Recently, Schwartz et al¹⁰ have validated a new equation to estimate eGFR called the "bedside Schwartz equation" based on the IDMS analysis that is now considered the gold standard.²²⁻²⁴ At the time of data collection, serum creatinine data were analyzed by using the Jaffe method. Therefore, it would be inappropriate for us to estimate eGFR based on the bedside Schwartz equation, given the differences in methodology in determining SCr.

As noted, there is no currently accepted definition of AKI in the pediatric cardiac ICU population. In the present study, we used a surrogate definition for vancomycin-associated AKI consistent with that in a previously published study. The pRIFLE is a validated tool that has

been developed to assess the development of AKI. Akcan-Arikan et al⁹ compared mortality outcomes as a function of different methods to assess AKI, including SCr or UOP, versus the combination of UOP and SCr. They found SCr had a stronger association with mortality than the other variables and suggested that it may be difficult to diagnose early AKI based on UOP alone. The clinical application of this scoring tool in patients undergoing CTS requires further study.^{6,9,21}

Despite these limitations, this study provides valuable data regarding the use of a protocol in select populations and the need for additional monitoring of vancomycin concentrations in the CTS population. As noted, these data were collected from 2008 to 2009, and we acknowledge there have been advances in the care of critically ill children since then. However, we believe that results from our pharmacokinetics analysis would still be valid even with these advances. We believe our projected vancomycin dosages can be used to aid clinicians until further studies are conducted. It should be noted that these are only projections and need to be validated. A future study should assess the likelihood of achieving an AUC:MIC ≥ 400 by using these dosage projections in pediatric CTS patients receiving vancomycin versus an age-matched control of pediatric CTS patients not receiving vancomycin.

CONCLUSIONS

A vancomycin dosage protocol of 20 mg/kg/dose IV every 8 hours achieved higher trough concentrations in pediatric CTS patients than in controls. Trough concentrations of 10 to 20 mg/L were attained in >50% of CTS patients. Vanco-

mycin pharmacokinetic parameters were noted to be highly variable in CTS patients, indicating more individualization of dosage is needed. Based on pharmacokinetic parameters, dosage projections for CTS were developed to target an AUC:MIC ≥ 400 . A future prospective study is needed to determine whether these proposed dosage regimens achieve AUC:MIC targets and whether these regimens are associated with the development of less vancomycin-associated AKI.

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Abbreviations AKI, acute kidney injury; AUC, area under the curve; CL, clearance, CPB, cardiopulmonary bypass; CTS, Cardiothoracic surgery; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; EMR, electronic medical record; IDSA, Infectious Diseases Society of America; IV, intravenous; K_{el} , elimination rate fitted for the pharmacokinetics program; K_{el} , elimination rate; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; SCr, serum creatinine; UOP, urine output; V_d , volume of distribution, in L/kg, fitted for the pharmacokinetics program; VD, volume of distribution in liters.

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