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Vancomycin dosing required to achieve a therapeutic level in children post-surgical correction of congenital heart disease

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Abstract

The vancomycin dosing range for safe and effective treatment remains uncertain for children who had corrective surgery for a congenital heart disease (CHD). We aimed to determine the vancomycin dosing requirements for this subgroup of patients.

This prospective cohort study included children younger than 14 years old with CHD who received intravenous vancomycin for at least 3 days at the Pediatric Cardiology section of King Abdulaziz Medical City, Riyadh.

In total, 140 pediatric patients with CHD were included with a median age of 0.57 years (interquartile range 0.21–2.2). The mean vancomycin total daily dose (TDD), 37.71 ± 6.8 mg/kg/day, was required to achieve a therapeutic trough concentration of 7–20 mg/L. The patient's age group and the care setting were significant predictors of the vancomycin dosing needs. Neonates required significantly lower doses of 34 ± 6.03 mg/kg/day (P = .002), and young children higher doses of 43.97 ± 9.4 mg/kg/day (P = .003). The dosage requirements were independent of the type of cardiac lesion, cardiopulmonary surgery exposure, sex, and BMI percentile. However, the patients in the pediatric cardiac ward required higher doses of vancomycin 41.08 ± 7.06 mg/kg/day (P = .039). After the treatment, 11 (8.5%) patients had an elevated S_{cr}, and 3 (2.3%) patients developed AKI; however, none of the patients' sociodemographic factors or clinical variables, or vancomycin therapy characteristics was significantly associated with the renal dysfunction.

Overall, the vancomycin TDD requirements are lower in pediatric post-cardiac surgery compared to non-cardiac patients and are modulated by several factors.

Abbreviations: AKI = acute kidney injury, AUC = area-under-the-curve, CHD = congenital heart disease, CL = clearance, CPB = cardiopulmonary bypass, ECMO = extracorporeal membrane oxygenator, MIC = minimum inhibitory concentration, MRSA = methicillin-resistant *Staphylococcus aureus*, PCICU = pediatric cardiac intensive care unit, PCW = pediatric cardiac ward, TDD = total daily dose, TTT = time to therapeutic trough, VD = volume of distribution.

Keywords: cardiology, congenital heart disease, pediatrics, pharmacokinetics, vancomycin

1. Introduction

Vancomycin, a glycopeptide compound, is a bactericidal antibiotic that inhibits the synthesis of the cell wall of gram-positive bacteria.[1,2] Vancomycin is widely used to treat infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (e.g., complicated skin and bone infections, bacteremia, endocarditis, and meningitis).[3] Typically, the initial vancomycin dose is from 40 to 60 mg/kg/day, divided every 6 to 8 hours. The dose is adjusted based on the target trough level. However, current literature reports that the total daily doses (TDDs) below 60 mg/kg are inadequate to achieve the desired vancomycin trough concentration (7–10 mg/L) or the target area-under-the-curve (AUC > 400 mg/h/L). Such target values are often required to treat MRSA strains with a vancomycin MIC ≤ 1 mg/L.[4–10] In addition, dosing requirements vary for each pediatric age group, with younger children requiring higher doses per body weight. However, limited data are currently available to support the specific dosing regimens for different pediatric subgroups.[4,6,9,11]

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A recent consensus guideline of the American Society of Health-System Pharmacists (ASHP), Infectious Disease Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) suggests a daily dose of 60 to 80 mg/kg vancomycin for children younger than 12 years old and a 60 to 70 mg/kg dose for children aged 12 years and older to be given in divided doses to achieve the target AUC level required for the treatment of MRSA strains with a MIC ≤1 mg/L. These recommendations were not based on pediatric data, but were extrapolated from research studies with adults.[12] The estimation of the AUC for monitoring vancomycin therapy is a useful pharmacodynamic surrogate marker used to predict drug safety and efficacy.[13,14] Although this approach has been adopted in some medical centers, trough concentration is still widely used in clinical practice as a surrogate marker of the AUC/MIC ratio for vancomycin monitoring because it correlates quite well with the AUC.[12,15] The serum trough concentration is obtained at the steady-state condition which is generally achieved before the fourth dose. The recommended target trough level is 10 to 15 mg/L for general indications, and 15 to 20 mg/L for complicated infections.[3,16] The peak level is not routinely done due to a lack of clinical correlation.

Nephrotoxicity is a major concern of vancomycin therapy and is mainly associated with higher trough concentrations >15 mg/L, and a prolonged treatment duration (>4 days). Although this side effect is well documented with vancomycin, other factors such as preexisting renal dysfunction, critical illness, and concurrent use of nephrotoxic drugs strongly contribute to an increased incidence.[17–25] To ensure the safety and efficacy of the vancomycin, many pediatric care centers develop a successful prescribing guideline for the initiation and subsequent monitoring of this drug.[26]

Variations of vancomycin pharmacokinetics have been reported in children with certain characteristics and disease states. For instance, a lower serum trough level of 7 to 10 mg/L is, unlike adults and older children, highly predictive of an AUC >400 in neonates and infants younger than 3 months.[27,28] However, burns enhances vancomycin clearance (CL) and increases the dosage requirement.[29,30] Other sources reported variability in cancer patients and critically ill children.[31–33] Changing vancomycin pharmacokinetics in children post-cardiac surgery is also possible. Alteration in renal perfusion, drug volume of distribution (VD), and CL, in addition to aggressive use of diuretics, necessitate close monitoring of the vancomycin level. Two retrospective studies with children following heart surgery suggested the use of vancomycin in doses lower than the generally recommended doses for the pediatric population between 20 and 40 mg/kg/day.[15,34]

To our knowledge, few studies investigated the appropriate vancomycin dosing for children post corrective surgery of congenital heart disease (CHD), and the vancomycin dosing range for safe and effective treatment remains uncertain for this subgroup of children. We conducted this prospective study to determine the dosing requirements of vancomycin for pediatric patients post-cardiac surgery.

2. Methods

2.1. Design and settings

This was a single-center prospective cohort study conducted at the Pediatric Cardiology Section of King Abdulaziz Medical City, Riyadh; an American College of Cardiology international center for excellence.[35] This center provides tertiary level care for children with complex congenital and acquired heart diseases.

2.2. Patient selection

All the children post-surgical correction of CHD receiving intravenous vancomycin from November 2019 to November 2020, at the pediatric cardiac intensive care unit or pediatric cardiac ward were screened for eligibility. The patients were included if they were 14 years old or younger and received intravenous vancomycin for at least 3 days. However, patients were excluded if they had a preexisting chronic or acute kidney disease, have been receiving renal replacement therapy or extracorporeal membrane oxygenator (ECMO), or the drug duration was less than 3 days. Patients could only be included once during the study period. If the same patient received the drug during 2 separate events, the latter event was not counted regardless of the time interval between the 2 incidents.

2.3. Outcome measures

The hospital's electronic health information system was the primary source for data collection. Researchers checked the records of all the patients admitted to the pediatric wards daily. Whenever a vancomycin order was identified, the child was promptly added to the data collection sheet, assigned a serial number, and screened for eligibility. For eligible children, age, weight, height, sex, comorbidities, cardiac lesion type, and concomitant nephrotoxic medications were recorded. Fever and pertinent laboratory values (WBC, platelet count, ESR, CRP, S_{cr}, BUN), and culture results were recorded at baseline and daily when available. The details of vancomycin therapy were collected throughout the treatment course, including the indication, initial dose and frequency, first trough level at steady state, number of dosage adjustments, and duration of therapy. In case of a regimen adjustment, the same details associated with the new regimen were recorded. The serum vancomycin concentrations were measured and analyzed at the chemistry laboratory of our institution using the particle-enhanced turbidimetric inhibition immunoassay method (Siemens Dimension; Dade Behring, Deerfield, Illinois, PETINIA).

The primary outcome of this study was to determine the vancomycin TDD (mg/kg/day) required to achieve a serum trough concentration between 7 and 20 mg/L and the incidence of vancomycin-associated acute kidney injury (AKI), defined as an absolute increase in S_{Cr} of ≥0.3 mg/dL, or a percentage increase in S_{Cr} exceeding 50% (1.5-fold) from the baseline at day 3, day 6, and post-treatment.[36] The secondary outcomes were the time to therapeutic trough (time needed to reach therapeutic level and the number of adjustments), in addition to studying the extent of the resolution of signs of the infection (fever, WBC, Platelet, ESR, CRP) on days 3 and 6.

2.4. Sample size calculation

In a study conducted by Thomas et al to determine the optimal vancomycin dosing regimen in pediatric CHD patients, therapeutic troughs were achieved in 50.6% of patients.[15] Using OpenEpi, the minimally required sample size was determined to be 112 as 156 pediatric cardiac patients received vancomycin during the study period, with the confidence level at 95% and the margin of type 1 error set as 5%.

2.5. . Ethical considerations

This study was reviewed and approved by the Institutional Review Board at King Abdullah International Medical Research Center (Study approval # SP18/197/R).

2.6. Statistical analysis

The data were analyzed using SPSS version 25.0. The quantitative data are reported as mean ± SD or as median (interquartile range [IQR]) for skewed data, and the qualitative data as frequencies. Wilcoxon's test was used to track the changes in nominal variables over 2 separate readings. Student-t-test or Mann-Whitney's test was used to analyze the association

between the quantitative (i.e., TDD, trough level) and binomial categorical variables, while χ^2 test was used for categorical data. A *P*-value of <.05 was considered statistically significant.

3. Results

Figure 1 demonstrates the study's flow diagram with 140 of the 156 initially screened patients enrolled in this study. The median age of the participants was 0.57 years (IQR: 0.21–2.2). Almost half of the sample were infants and 25.7% (n = 36) young children (Table 1). An approximately equal percentage was included from both genders. The median weight was 5.5 kg (IQR: 3.4–10.97), and more than half of the patients (57.9%, n = 81) were underweight, 55 (39.3%) patients had a normal weight, and a small proportion was overweight or obese (2.8%, n = 3).

The baseline clinical data are presented in Table 1. The cardiac lesions were primarily acyanotic (60%, n = 84), more than two-thirds of the patients (69.3%, n = 97) received cardiopulmonary bypass (CPB) surgery, and an approximately equal proportion of patients received the drug while admitted to the intensive care unit (ICU) or non-ICU regular ward units. Nephrotoxic medication use was frequent when the vancomycin was initiated. Furosemide was the most used nephrotoxic drug (91.4%, n = 128), followed by ACE inhibitors (68.6%, n = 96), ceftazidime (58.6%, n = 82), and spironolactone (35%, n = 49). At baseline, the majority of patients had fever (57.1%, n = 80), negative blood culture (43.6%, n = 61), slightly increased WBC (12.7 ± 6.14 × 10^9/L), and an increased CRP (2.6 mg/dL (IQR: 0.9–7.4) and (BUN 12.43 mg/dL ± 6.16).

Vancomycin therapy was prescribed empirically (80.7%, n = 113), or because of fever (37.9%, n = 53), followed by clinical deterioration (19.3%, n = 27), or sepsis (14.3%, n = 20). Most cultures were negative for causatives microbes (78.6%, n = 110), only 8 (5.7%) had MRSA and 5 (3.6%) enterococcus.

The mean initial vancomycin dose received was 36.7 ± 6.6 mg/kg/day divided every 6 hours (65.7%, n = 92), or every 8 hours (32.1%, n = 45). The mean treatment duration was 6.4 ± 4.8 days.

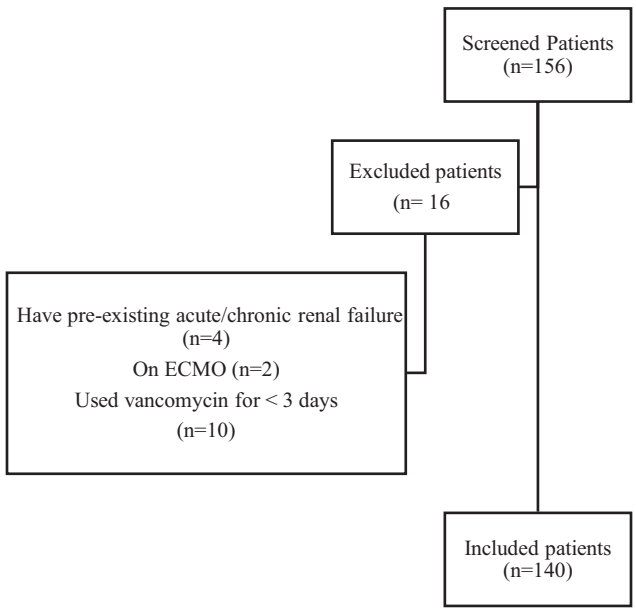

Figure 1. The study's flow diagram.

Table 1

Patients' baseline characteristics and the characteristics of vancomycin therapy (N = 140); n (%) unless otherwise stated.

Demographic		
Age (years)	Median (IQR)	0.57 (0.21–2.2)
Age category, n (%)	Neonates	16 (11.4)
	Infants	71 (50.7)
	Young child (1–6 years)	36 (25.7)
	Old child (>6–14 years)	17 (12.1)
Sex, n (%)	Female	68 (48.6)
	Male	72 (51.4)
Weight (kg)	Median (IQR)	5.5 (3.4–10.97)
BMI* percentile (category), n (%)	<5th (underweight)	81 (57.9)
	≥5th to 85th (normal weight)	55 (39.3)
	≥85th to 95th (overweight)	1 (0.7)
	≥95th (obese)	3 (2.1)
Baseline clinical data		
Cardiac lesion, n (%)	Acyanotic	84 (60)
	Cyanotic	56 (40)
CPB surgery exposure, n (%)	Exposed	97 (69.3)
Setting, n (%)	ICU	72 (51.4)
	Non-ICU	68 (48.6)
Nephrotoxic medication, n (%)	Piperacillin/tazobactam	11 (7.9)
	Meropenem	36 (25.7)
	Aminoglycosides	20 (14.3)
	Ceftazidime	82 (58.6)
	Amphotericin B	2 (1.4)
	Furosemide	128 (91.4)
	Angiotensin-converting enzyme Inhibitors (ACEI)	96 (68.6)
	Spironolactone	49 (35)
	Colistin	1 (0.7)
Baseline lab data		
Fever, n (%)	Positive	80 (57.1)
Culture, n (%)	Negative	61 (43.6)
	Positive	24 (17.1)
	Not available	55 (14)
WBC × 10^9/L	Mean (±SD)	12.7 ± 6.14
Platelet count × 10^9/L	Mean (±SD)	315.3 ± 199.9
ESR (mm/hr)	Median (IQR)	9 (3–20)
CRP (mg/dL)	Median (IQR)	2.6 (0.9–7.4)
S_{cr} (mg/dL)	Mean (±SD)	0.45 ± 0.09
BUN (mg/dL)	Mean (±SD)	12.43 ± 6.16
Vancomycin therapy		
Indication, n (%)	Therapeutic	24 (17.1)
	Empirical	113 (80.7)
	Prophylaxis	3 (2.1)
Infection type, n (%)	Fever	53 (37.9)
	Endocarditis	8 (5.7)
	Bacteremia	11 (7.9)
	Pneumonia	4 (2.9)
	Sepsis	20 (14.3)
	Urinary tract infection (UTI)	3 (2.1)
	Osteomyelitis/cellulitis	2 (1.4)
	Skin infection	1 (0.7)
	Wound infection	9 (6.4)
	Central line infection	2 (1.4)
	Clinical deterioration	27 (19.3)
Culture, n (%)	No positive culture	110 (78.6)
	MSSA	4 (2.9)
	MRSA	8 (5.7)
	S. epidermidis	11 (7.9)
	Enterococcus	5 (3.6)
	Streptococcus	2 (1.4)
Dose-initial (mg/kg/day)	Mean (±SD)	36.7 (6.6)
	Mode	40
Dose category, n (%)	>45 mg/kg/day	4 (2.9)
	40 ± 5 mg/kg/day	86 (61.4)
	<35 mg/kg/day	50 (35.7)
Frequency category, n (%)	Q6	92 (65.7)
	Q8	45 (32.1)
	Q12	2 (1.4)
	Q24	1 (0.7)
Duration of therapy (days)	Mean (±SD)	6.4 ± 4.8

*CDC BMI (age ≤ 24 months), or CDC weight-for-length (age > 24 months).

The mean vancomycin TDD required to achieve a serum trough concentration between 7 and 20 mg/L was 37.71 ± 6.8 mg/kg/day (Table 2). The required vancomycin doses were modulated by different factors, the neonates required significantly lower doses (34 ± 6.03 mg/kg/day, $P = .002$) and the young children higher doses (43.97 ± 9.4 mg/kg/day, $P = .003$). The dosage requirements did not differ between gender, or BMI percentile categories. The dosage requirements were also independent of the type of cardiac lesion and exposure to CPB surgery. However, the non-ICU patients required higher doses of vancomycin to reach therapeutic levels (41.08 ± 7.06 mg/kg/day, $P = .039$).

Table 3 demonstrates the change in renal function following treatment initiation and post-treatment. At day 3, 96 (96%) of the sample had a normal S_{cr} with only 4 (4%) an elevated S_{cr}. However, elevated S_{cr} cases were more frequent on day 6 (8%, n = 4), and post-treatment (8.5%, n = 11). AKI was only observed after treatment in 3 (2.3%) patients.

Table 4 presents the possible factors that may affect the incidence of AKI and S_{cr} elevation. None of the sociodemographic factors (age, BMI percentile) or clinical variables (cardiac lesion type, CPB exposure, concurrent nephrotoxic medications, or care setting), vancomycin therapy characteristics (TDD, trough level, duration of therapy, or frequency of administration) was significantly associated with the occurrence of AKI or S_{cr} elevation.

Table 5 displays the number of days and dosage adjustments to reach target therapeutic levels. Around half of the patients (55.7%, n = 78), achieved the target trough levels without any dosage adjustments; a third (30%, n = 42) necessitated a single adjustment. The majority of the patients (69.3%, n = 97) required 2 days to reach the target level, with 29 (20.7%) requiring 3 days.

The change in the signs of infection and laboratory data by days 3 and 6 are reported in Table 6. No significant change was reported on days 3 and 6 in WBC, platelets counts and ESR levels. However, the CRP was significantly increased on day 3 to 3.5 mg/dL (IQR: 1.3–7.0) ($P = .041$), followed by a significant reduction on day 6 to 1.4 mg/dL (IQR: 0.9–4.1) ($P = .013$). Fever cases were also decreased on days 3 and 6 successively ($P < .001$).

4. Discussion

In this study, the mean vancomycin TDD required to achieve therapeutic trough concentrations for pediatric cardiac patients were lower than the recommended dosing. The vancomycin therapy pharmacokinetics was affected by several attributes of this subgroup of patients such as altered renal perfusion, drug distribution, drug CL, in addition to aggressive use of diuretics.

Literature reports a few studies regarding the safe, effective, and optimal vancomycin dosing regimen for pediatric patients with CHD.[15,22,34,37,38] Although not verified yet, Marlowe et al suggested that the vancomycin pharmacokinetic variables (e.g., Vd and elimination half-life) are similar between cardiac and non-cardiac pediatric patients.[34] However, pediatric cardiology patients are susceptible to changes in the vancomycin pharmacokinetics, possibly due to varying body functioning between the age groups or the questionable impact of CHD.[39] More importantly, several nephrotoxic medications are often administered to CHD patients as a part of the treatment plan, which may affect the safety of the vancomycin and obtained vancomycin levels.[40] Many patients in the current report were concurrently taking such agents (e.g., furosemide, ACE inhibitors, ceftazidime, and spironolactone), supporting the analysis of the dosing requirements and the variables necessitating changes.

Table 2

Sociodemographic and clinical variables affecting the total daily dose requirements to achieve the target level; n (%) unless otherwise stated (n = 114).

Sociodemographic and clinical variables		TDD required to achieve the target level (Mean ± SD)	p-value
Reference		37.71 ± 6.8	Reference
Age category			0.001
	Neonates (n = 15)	34 ± 6.03	0.002
	Infants (n = 61)	37.84 ± 6.2	0.033
	Young child (n = 29)	43.97 ± 9.4	0.003
	Old child (n = 7)	35.7 ± 11.3	0.723
Sex, n (%)	Female (n = 62)	38.32 ± 9.02	0.12
	Male (n = 52)	40.76 ± 7.17	
BMI* percentile (category), n (%)	<5th (underweight) (n = 66)	38.75 ± 7.55	0.305
	≥ 5th to 85th (normal) (n = 46)	40.38 ± 9.4	0.314
	Overweight-obese (n = 2)	40	0.807
Cardiac lesion, n (%)	Acyanotic (n = 64)	38.59 ± 8.13	0.22
	Cyanotic (n = 50)	40.5 ± 8.43	
CPB surgery exposure	Non-exposed (n = 37)	38.4 ± 7.3	0.348
	Exposed (n = 77)	39.94 ± 8.7	
Setting	ICU (n = 59)	37.89 ± 9.07	0.039
	Non-ICU (n = 55)	41.08 ± 7.06	

*CDC BMI (age ≤ 24 months), or CDC weight-for-length (age > 24 months.

Table 3

The change in renal function on days 3 and 6 and post-treatment; N (%) unless otherwise stated.

	Renal function test	Baseline	Day 3 (n = 100), N (%)	Day 6 (n = 50), N (%)	Post-treatment† (n = 129), N (%)
Change in S_{cr}	Less than 25% increase in S_{cr}(normal)	Reference	96 (96%)	46 (92%)	115 (89.1%)
	25–50% increase in S_{cr} (elevated)	Reference	4 (4%)	4 (8%)	11 (8.5%)
	>50% increase in S_{cr} (AKI)	Reference	0	0	3 (2.3%)
BUN level	mean (±SD)	4.44 ± 2.24	4.17 ± 2.44	4.42 ± 3.98	4.39 ± 2.77

†S_{cr} 24–48 hours after completion of the treatment course

Table 4

Variables affecting the incidence of vancomycin-associated acute kidney injury (AKI) and elevated serum creatinine; N (%) unless otherwise stated

Variables		AKI (n = 3), N (%)	*P*-value*	elevated S_{cr} (n = 15), N (%)	*P*-value*
Total daily dose (mg/kg/day)	Mean (±SD)	42.5 ± 3.5	0.517	36.15 ± 6.5	0.878
Trough levels of vancomycin	Mean (±SD)	9.25 ± 3.9	0.54	8.17 ± 4.08	0.115
Duration of therapy	Mean (±SD)	7.67 ± 2.8	0.67	7.2 ± 5.96	0.55
Frequency	q24h (n = 1)	0	0.97	0	0.88
	q12h (n = 1)	0	0.97	0	0.78
	q8h (n = 44)	2 (66.7)	0.26	5 (33.3)	0.65
	q6h (n = 83)	1 (33.3)	0.28	10 (66.7)	0.93
Concomitant nephrotoxic medication, n (%)	Piperacillin/tazobactam (n = 9)	0	0.804	1 (6.7)	0.69
	Meropenem (n = 36)	0	0.56	4 (26.7)	0.63
	Aminoglycosides (n = 20)	1 (33.3)	0.39	0	0.12
	Ceftazidime (n = 73)	3 (100)	0.26	11 (73.3)	0.18
	Amphotericin B (n = 2)	0	0.95	0	0.78
	Furosemide (n = 118)	3 (100)	0.76	14 (93.3)	0.64
	Angiotensin-converting enzyme inhibitors (ACEI) (n = 89)	1 (33.3)	0.23	8 (53.3)	0.23
	Spironolactone (n = 47)	1 (33.3)	0.7	4 (26.7)	0.43
	Colistin	0	0.97	0	0.88
Age category	Neonates (n = 16)	1 (33.3)	0.33	1 (6.7)	0.47
	Infants (n = 70)	2 (66.7)	0.56	11 (73.3)	0.12
	Young child (n = 30)	0	0.45	2 (13.3)	0.35
	Old child (n = 11)	0	0.76	1 (6.7)	0.64
BMI† percentile (category), n (%)	Underweight (n = 75)	1 (33.3)	0.57	6 (40)	0.11
	Normal (n = 50)	2 (66.7)	0.55	8 (53.3)	0.19
	Overweight-obese (n = 4)	0	0.9	1 (6.7)	0.38
Cardiac lesion	Cyanotic (n = 52)	1 (33.3)	0.64	8 (53.3)	0.24
CBP surgery exposure	Exposed (n = 84)	3 (100)	0.55	10 (66.7)	0.53
Setting, n (%)	ICU (n = 68)	2 (66.7)	0.56	9 (60)	0.56
	Non-ICU (n = 58)	1 (33.3)		6 (40)	

*Compared to patients with normal renal function.

†CDC BMI (age ≤ 24 months), or CDC weight-for-length (age > 24 months).

Table 5

Number of days and dosage adjustments to reach target therapeutic levels.

Variable		N(%)
Number of adjustments	0 = no adjustment	78 (55.7%)
	1 = once	42 (30%)
	2 = twice	12 (8.6%)
	3 = thrice	6 (4.3%)
	4 = four times	1 (0.7%)
	5 = five times	1 (0.7%)
Number of days to reach the first target level	1 day	97 (69.3%)
	2 days	29 (20.7%)
	>2 days	14 (10%)

Vancomycin is usually administered in doses ranging between 40 and 60 mg/kg/day divided every 6 to 8 hours. More recently, a higher vancomycin TDD was recommended for children because of the inadequacy of doses lower than 60 mg/kg/day to achieve the desired trough levels. However, the altered CHD patient pharmacokinetics, due to the changed kidney function or fluid overload with the varying pharmacokinetic profile of the pediatric population, is not always considered when projecting these guidelines. In this study, the majority of the patients received a vancomycin dose between 35 and 45 mg/kg/day divided every 6 hours. The mean vancomycin TDD required to achieve a serum trough concentration between 7 and 20 mg/L was 37.71 ± 6.8 mg/kg/day. This dose is much higher than that reported by Marlowe et al with an initial vancomycin dose of 10 mg/kg/dose every 12 hours was optimal to achieve therapeutic trough concentration (5–10 mg/L) in CHD patients.[34] However, our study and Marlowe's findings oppose what is recommended by the consensus statement of the IDSA/ASHP/SIDP 2020 (60–80 mg/kg for children <12 years old and 60–70 mg/kg children >12 years).[12]

It is noteworthy that the required vancomycin TDD to achieve the therapeutic outcomes was highly dependent on the age group, as was previously noted in a similar study by Thomas et al.[15] Neonates enrolled in this study required significantly lower doses (34 ± 6.03 mg/kg/day, $P = .002$), infants (37.84 ± 6.2 mg/kg/day) and young children (1–6 years) required higher doses

Table 6

The change in signs of infection and lab data by days 3 and 6.

	Baseline (n = 140) *	D3 (n = 140)	*P*-value	D6 (n = 84)	*P*-value
Fever, n (%)	80 (57.14)	23 (16.4)	<0.001	13 (15.4)	<0.001
WBC, median (IQR)	11.45 (8.5–15.14)	11.4 (7.7–15.1)	0.111	11.7 (9.3–14.7)	0.958
Platelet, median (IQR)	298 (188–398.25)	253 (157.5–405.5)	0.49	250.5 (159.75–421.75)	0.705
CRP, median (IQR) (mg/L)	2.6 (0.9–7.4)	3.5 (1.3–7.0)	0.041	1.4 (0.9–4.1)	0.013
ESR, median (IQR) (mm/hr)	9 (3–20)	7.5 (2.75–30.25)	0.414	24 (9–64.75)	0.125

*Reference.

(43.97 ± 9.4 mg/kg/day, $P = .003$). The findings echo Thomas et al's recommendations to empirically load patients with CHD, with a normal renal function, with the following doses: 30 mg/kg/day for neonates, 35 to 40 mg/kg/day for infants, and 45 mg/kg/day in children to be divided every 6 to 8 hours.[15] This dosing variation may be due to the lower glomerular filtration rate in neonatal kidneys compared to other age groups; the CL of renally excreted vancomycin is greatly affected and lower doses are required compared to older children.[41]

Surprisingly, the non-ICU patients required the use of higher vancomycin doses (41.08 ± 7.06, $P = .039$). The patients admitted in an ICU often have compromised cardiac circulation causing a reduced renal and hepatic perfusion which necessitates lower dosing. This is especially true for 2-compartment-model drugs, such as vancomycin.

In a review conducted by Grace, the vancomycin dosing in obese patients was altered compared to non-obese patients.[42] This may be caused by an increased VD due to the increased adipose tissue and muscle mass.[42] In addition, obese patients have an increased glomerular filtration rate due to an increased renal plasma flow.[42] Exposure to CPB surgery was also associated with an increased vancomycin systemic CL ($P < .0005$) in the Gracia et al study,[43] and it would be expected to have increased dosing requirements for obese and CPB-exposed patients. However, the vancomycin's TDD requirements (i.e., vancomycin CL) were relatively independent of sex ($P = .12$), CPB surgery exposure ($P = .348$), BMI percentile category ($P > .05$), and the type of cardiac lesion ($P = .22$), which supports Thomas et al's findings.[15]

Literature frequently suggests that vancomycin may be associated with nephrotoxicity; however, a direct cause-effect relationship has not yet been determined.[25] In this study, 8.5% of the patients had an elevated S_{cr} and 2.3% developed AKI post-vancomycin treatment. This is slightly lower than the incidence of vancomycin-associated AKI reported by Moffett et al as 7.2% of the sample developed AKI.[22] Similarly, a higher incidence, 14% of 167 patients receiving vancomycin, was recorded by Mckamy et al in the general pediatric population.[25] In general, vancomycin-associated AKI is less frequent in children compared to adults, as concluded by Moffett et al, affecting 12 to 42% of the adult population, especially when concurrently administered with aminoglycosides.[22,25]

In our study, none of the sociodemographic factors (age, BMI percentile) or clinical variables (cardiac lesion type, CPB exposure, concurrent nephrotoxic medications, or care setting), vancomycin therapy characteristics (TDD, trough level, duration of therapy, or frequency of administration) was significantly associated with the occurrence of AKI or S_{cr} elevation. Similarly, exposure to cardiac surgery and serum vancomycin levels were not independent predictors for vancomycin-associated AKI in Moffett et al's report; however, higher vancomycin dosing requirements were significantly associated with AKI occurrence, independent of the serum drug level.[22] This is surprising as pediatric cardiac surgery patients are especially vulnerable to AKI which affects approximately 40 to 50% of the cases, primarily because of fluid disturbances and changed drug metabolism and other causes.[44] It has also been noted by Mckamy et al that nephrotoxicity was associated with supratherapeutic trough levels (OR: 3.27 [95% confidence interval: 1.19–8.95], $P = .021$) and furosemide administration in the ICU (OR: 9.45 [95% confidence interval: 3.44 to 26.00], $P < .0001$).[25] In addition, a meta-analysis by Fiorito et al reported that higher trough levels (≥15 mg/L), baseline renal impairment, dehydration, and concurrent use of nephrotoxic medications are possible predictors of vancomycin-associated nephrotoxicity in the pediatric population.[21]

In summary, the currently recommended vancomycin dosing (40 mg/kg divided every 6–8 hours) coincides with the most appropriate dosing (37.71 ± 6.8 mg/kg/day); that is, it is both safe and effective. However, this dosing should be modified by age, as is highlighted by our study, where neonates need lower doses (34 ± 6.03 mg/kg/day), and young children higher doses (43.97 ± 9.4 mg/kg/day). Dosage requirements were independent of sex, BMI percentile categories, type of cardiac lesion, and exposure to CPB surgery. It is also suggested that non-ICU patients may need higher vancomycin doses (41.08 ± 7.06 mg/kg/day). Renal function changes were independent of vancomycin dosing and trough levels.

Overall, cardiac patients enrolled in this study required lower vancomycin doses compared to the doses regularly dispensed. This may be due to the aggressive diuresis received by this population group as most of the patients were receiving furosemide. However, the TDD and trough levels were non-significantly changed between patients placed on diuretics or not. It is suggested in future studies that the VD and body fluid composition changes occurring in cardiac patients be measured. In this regard, the current physiologic status can be measured and correlated with dosing changes.

4.1. Strengths and limitations

This was a prospective cohort study investigating the optimal vancomycin dosing in pediatrics with CHD and different variables affecting dosing requirements with a relatively big sample size. One major limitation of the study design is its lack of a comparative control group (non-cardiac patients) which limits the conclusive correlations in the present study. The study was a single-center study that may not be representative of the general population. In addition, some key trough levels were missing which may have affected the study findings. Even though, our study addressed the effects of CPB exposure on the vancomycin dosing, it did not investigate the impact of the CPB time which potentially could affect the postoperative drug pharmacokinetics. In addition, the study included all eligible patients irrespective of their underlying genetic disorders that could affect the drug metabolism such as Down syndrome. Despite the big sample size, the number of patients developing AKI or overweight/obese patients remained low, which limits the generalizability of data about these subgroups. Although AKI occurred during the first week of therapy in McKamy et al's study, some adult studies suggested that nephrotoxicity may not be directly obvious until after 1 to 3 weeks,[25] and a follow-up Scr measurement would have been essential for more robust results.

5. Conclusion

Overall, pediatric CHD patients generally require a lower vancomycin TDD compared to the general pediatric population. The findings indicate that vancomycin should be administered to pediatric cardiology patients using a patient-specific dosing approach (age and care setting) rather than through a generalized dosing regimen (60 mg/kg/day divided every 6–8 hours) as previously suggested.

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