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Pharmacokinetics of Vancomycin in Pediatric Patients Receiving Intermittent Hemodialysis or Hemodiafiltration

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Introduction: Vancomycin is a common antibiotic used to treat hemodialysis (HD) or hemodiafiltration (HDF)-related infections in pediatric patients, but optimal dosing remains unknown. This is the first observational study to characterize the pharmacokinetics and evaluate dosing of vancomycin in this population.

Methods: Eligible patients received IV vancomycin 10 mg/kg per dose postdialysis followed by a series of serum vancomycin concentrations collected before, immediately after, 1 hour after, and 4 hours after dialysis. The pharmacokinetic parameters were estimated using 1- and 2-compartment models and a nonlinear least-squares algorithm.

Results: Among 42 vancomycin courses in 16 patients, 1 compartment model had the best fit for observed data. The net drug removal was 43 ± 13% (39% for HD and 50% for HDF) from an average 3-hour HD/HDF session. The mean elimination constant was 0.28 h^{-1} (standard deviation [SD], 0.11 h^{-1}) during the intradialytic period compared with 0.0049 h^{-1} (SD, 0.004 h^{-1}) when off dialysis. The mean volume of distribution was 0.65 (SD, 0.19) L/kg. Duration of dialysis session and mode of dialysis (HD vs. HDF) were significant predictors of vancomycin pharmacokinetic parameters. Half-life was shorter for HDF compared with HD (2.1 vs. 3.5 hours).

Conclusions: Based on the simulations, an initial vancomycin dose of 10 mg/kg per dose and redosing postdialysis was optimal to achieve a vancomycin concentration range of 5 to 12 mg/L at 4 hours postdialysis and 24-hour area under the curve over minimum inhibitory concentration of ≥400 hours. Therapeutic drug monitoring is necessary to account for residual variability in vancomycin elimination in pediatric patients receiving HD/HDF.

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Patients with end-stage renal disease (ESRD) are treated with renal replacement therapy such as hemodialysis (HD) or hemodiafiltration (HDF), or renal transplantation.[1,2] HDF, a newer mode of intermittent dialysis for pediatric patients, which enhances clearance of both large- and middle-molecular-weight solutes, and which may impact dialysis clearance of medications, was implemented in 2016 at The Hospital for Sick Children (SickKids) in Toronto, Ontario, Canada.[3,4]

Bacterial infections are one of the leading causes of hospitalization and mortality in pediatric patients receiving dialysis.[5–10] In the United States, the cumulative incidence of infection-related hospitalizations in pediatric dialysis patients was 22% (1996–2001).[7] In a Canadian cohort study, bacterial or viral infections were the cause of death in 8 of the 59 deaths (13.6%) that occurred in patients who had dialysis before first transplant.[5] Vancomycin is commonly used empirically or to treat documented proven infections because Gram-positive pathogens, such as *Staphylococcus* species, are responsible for most vascular access infections in patients undergoing HD.[11]

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Dialysis can play a significant role in vancomycin elimination in patients with ESRD. In the 1980s, when conventional HD utilized low-flux dialysis membranes, the elimination of vancomycin was minimal because of its larger molecular weight of 1446 Da compared with the typical drug molecular size (200–600 Da).[12,13] However, vancomycin has a relatively low protein-bound fraction (50%) and volume of distribution (V_d) of 0.6 L/kg, which makes it available to diffuse through dialyzer membranes.[14] Since the 1990s, low-flux dialyzers have largely been replaced by high-flux dialyzers that have been found to eliminate vancomycin more efficiently, ranging from 17% to 49.5% in 4 hours.[12] It remains unknown whether HDF further increases elimination compared with high-flux HD.

A 24-hour area under the concentration–time curve/minimal inhibitory concentration ratio (AUC/MIC) of at least 400 hours was found to be the most important pharmacodynamic parameter in predicting activity of vancomycin against *Staphylococcus* and has been advocated for use in a recent consensus guideline.[13,15,16] However, associations between AUC/MIC target and outcomes have not been validated in the HD/HDF population and non–methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Serum vancomycin trough concentration is often used in pediatric practice since the time when associations were first demonstrated between AUC/MIC and trough concentration.[13,17,18] A vancomycin trough concentration of >15 mg/L was found to be an independent risk factor for nephrotoxicity.[19] Therefore, SickKids' vancomycin trough target ranges are 10 to 15 mg/L for infections of the central nervous system (CNS) or the treatment of more resistant, invasive pathogens such as MRSA, and 5 to 12 mg/L for other infections.[20]

Four case reports have described vancomycin use in the pediatric population receiving intermittent HD/HDF—3 of them describing dialysis to treat an overdose of vancomycin.[21–23] The remaining case report described a 6-year-old anephric female on long-term HD who was given vancomycin to treat staphylococcal bacteremia.[24] The Bayesian nonlinear least-squares algorithm and single-compartment model was used to estimate vancomycin pharmacokinetics (PK). The half-life off dialysis ($t_{1/2,\text{interdialytic}}$) was 99 hours and on dialysis ($t_{1/2,\text{interdialytic}}$) was 6 hours. The authors adjusted doses to achieve a peak vancomycin concentration of 25 to 30 mg/L and trough concentration of 10 to 15 mg/L, and recommended a loading dose of 15 mg/kg IV vancomycin followed by dose adjustments using therapeutic drug monitoring (TDM) to establish vancomycin PK before determining an optimal dosing schedule. However, their investigation was a historic study using a C-DAK 2500 dialyzer (a low-flux hollow-fiber dialyzer made of cuprophan, manufactured by Cordis Dow), which is no longer used in clinical practice.

Overall, there was a lack of information regarding vancomycin removal in pediatric patients receiving intermittent HD or HDF. Extrapolation of vancomycin dosing strategies from adult dialysis patients relies on the assumption that the PK between adult and pediatric populations are similar, but this is inappropriate due to significant differences in physiology and PK parameters.[25] Therefore, the aim of our study was to investigate vancomycin pharmacokinetics and determine the best dosing strategy in children on HD/HDF. Our primary objective was to characterize vancomycin PK in pediatric patients receiving HD/HDF. Our secondary objectives were to monitor efficacy and safety of each course, explore the effects of patient- and HD/HDF-related characteristics on the PK parameters, and develop dosing recommendations based on Monte Carlo simulations (MCSs) for pediatric patients on HD/HDF to maximize the probability of target attainment (PTA) for trough concentrations of 5 to 12 mg/L (non-CNS infections) or 10 to 15 mg/L (CNS infections) and PTA of 24-hour AUC/MIC ratio of ≥400 hours.

METHODS

This was a single-center, retrospective study that included pediatric patients (age < 18 years) admitted to SickKids (inpatient ward and dialysis clinic) between January 1, 2015 and February 6, 2017, who received intermittent HD/HDF and were prescribed IV vancomycin for empiric or documented infections. Patients receiving either peritoneal dialysis or continuous renal replacement therapy were excluded. This study was carried out in accordance with the ethical principles of the Declaration of Helsinki and approved by the SickKids research ethics board and by an administrative review panel through the Office of Research Ethics at the University of Toronto. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[26]

Therapeutic Drug Monitoring

Serum vancomycin concentrations were analyzed by an immunoassay (Viva-Emit, Dade Behring, Deerfield, IL) with coefficients of variation for imprecision at low-, medium-, and high-quality control levels of 5.1%, 4.7%, and 5.5%, respectively. The lower limit of quantification was 5 mg/L. A TDM practice guideline for patients on HD/HDF prescribed vancomycin at SickKids in April 2016 was implemented to standardize vancomycin dosing and TDM. The guideline included administration of IV vancomycin at 10 mg/kg per dose postdialysis, based on recommendations from Aronoff's

renal dosing handbook.[27] Vancomycin doses were infused routinely over 1 hour, or overextended to 2 hours if the patient had red man syndrome, as per SickKids' IV drug guidelines. Subsequent dosing was guided by TDM from a series of blood samples drawn predialysis, immediately postdialysis, 1 hour postdialysis, and 4 hours postdialysis with each dialysis session. Patients were redosed if the 4-hour postdialysis concentration was within or below SickKids' trough target ranges.

Data Collection

Potential patients were identified from reports generated by the electronic pharmacy system version 9.2.36.33 (BDM IT Solutions, Inc, Saskatoon, SK, Canada) and screened for inclusion using electronic health information systems, including KidCare release 6.0 (Allscripts Sunrise Enterprise, Richmond, BC, Canada), Nephrology Data Warehouse (SickKids, Toronto, ON, Canada), and electronic patient charts. Data were managed using the Research Electronic Data Capture 7.2.2. tool, a secure, web-based application, hosted at SickKids.[28]

Pharmacokinetic Model

The primary endpoints were percentage of vancomycin removal, percentage of vancomycin rebound, elimination constant (k_e), half-life ($t_{1/2}$), and clearance (Cl) during intradialytic and interdialytic periods, and V_d in the interdialytic period. Initial estimates of the PK parameters were calculated based on a first-order, 1-compartment model using the observed vancomycin concentrations from each course (Supplementary Appendix). Vancomycin dosing regimens and PK parameters (e.g., V_d and Cl) were scaled to dry weight (clinically determined lowest weight without extra fluid that patients that can tolerate without symptoms during dialysis).

The PK parameter optimization was then performed using Excel Solver, which is based on the robust generalized reduced gradient nonlinear method.[29] Initial PK parameters were first preset to start an iterative process until optimal solutions for V_d, $k_{e,\text{interdialytic}}$, and $k_{e,\text{intradialytic}}$ were found when the residual sum of squares (RSS) converge to minimum (nonlinear least-square algorithm). RSS was determined by comparing the predicted and observed serum vancomycin concentrations according to:

$$RSS = \sum_{t=0}^{n} \left(C_t - \widehat{C}_t\right)^2$$

where C_t is the observed serum vancomycin concentration at time t since first dose given, $\hat{C}_t$ is the estimated serum vancomycin concentration at time t, and n is the number of observations.

A 2-compartment model was developed using Phoenix WinNonlin and the fit of this model was compared with the 1-compartment model to determine the model with best fit. The developed PK models were compared with the Akaike information criterion (AIC), Bayesian information criterion (BIC), and RSS, where the best model to fit the observed vancomycin concentrations was selected based on the lowest value of AIC, BIC, and RSS.

Statistical Analysis

Descriptive statistics (mean and standard deviation [SD] or median and interquartile range for continuous variables, frequency and proportion for categorical variables) were used to summarize patient and dialysis characteristics in Microsoft Excel 2013. Efficacy endpoints (changes in white blood cell [WBC] count, body temperature, and eradication of organisms based on microbiology results) and safety endpoints (vancomycin-related adverse events) were also described as an exploratory analysis.

The effects of the following variables on the PK parameters were evaluated using univariate linear regression analysis: age, sex, dry weight, duration of dialysis, frequency of dialysis, blood flow rate, dialysate flow rate, ultrafiltration rate, type of dialysis, type of dialyzer, urea reduction ratio (URR), and Kt/V (where K is the dialyzer's clearance of urea, t is dialysis duration, and V is volume of distribution of urea). A test for normality for each parameter was conducted using the Anderson-Darling and Shapiro-Wilk methods, with $P < 0.05$ considered significant.[30] The t test was used to assess for significance between 2 groups (HD vs. HDF) for normally distributed nominal data. The Wilcoxon rank sum test was used to assess data that were not normally distributed. The relationships between each factor and PK parameter were also assessed using scatterplots and determination of coefficient (R^2). Analysis of variance was used to determine P value for regression. $P < 0.05$ was considered statistically significant. Analyses were done using SAS version 9.4 (SAS Institute, Cary, NC).

Sample Size

Sample size was determined from $N = (Z\sigma/E)^2$, where Z is the value from the standard normal distribution reflecting the confidence level (e.g., $Z = 1.645$ for 90%), σ is the standard deviation of the parameter, and E is the desired margin of error.[31] A sample size of at least 9 courses of vancomycin was needed based on 90% confidence (type I error probability [α] = 0.10), margin of error of up to 25%, and the means and SDs

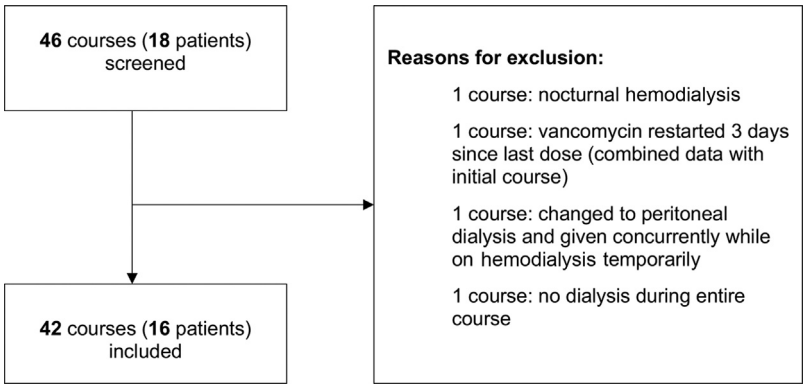

Figure 1. Screening for study inclusion.

for drug removal, drug rebound, V_d, $k_{e,\text{interdialytic}}$, and $t_{1/2,\text{interdialytic}}$ from the first 6 courses collected in the study.

Dosing Validation and Optimization

MCSs were performed to evaluate dosing of vancomycin using the Oracle Crystal Ball Classroom Edition release 11.1.2391.0 (Oracle Corp, Redwood Shores, CA). Simulations were conducted based on the mean and SD of the PK parameters determined from the final PK model: $k_{e,\text{intradialytic}}$, $k_{e,\text{interdialytic}}$, V_d, and percent rebound. The common infusion time of 1 hour and duration of dialysis session of 3 hours were kept constant for each MCS run. MCSs were repeated multiple times with different combinations of minimal inhibitory concentration (MIC) (0.5, 1, and 2 mg/L), dosing interval (every 24 hours [for patients receiving 1 dialysis session per day] and every 48 hours [for patients with 3 or 4 dialysis sessions per week]), loading doses (range, 6–39 mg/kg), and maintenance doses (range, 4–31 mg/kg). Each run had 10^6 simulations. The MCSs were then used to determine the PTA for trough concentrations of 5 to 12 mg/L (non-CNS infection) or 10 to 15 mg/L (CNS infection) by forecasting the 4-hour postdialysis concentrations and the PTA at 24-hour AUC/MIC ratio ≥400 hours for MICs of 0.5, 1, and 2 mg/L. These MIC values were chosen based on a review performed in the Department of Microbiology at SickKids, which ranged from ≤1 to 2 mg/L for *S aureus*, coagulase-negative *Staphylococcus*, and *Enterococcus* species (Y Yau, e-mail correspondence, The Hospital for Sick Children, 2017).[32]

RESULTS

Forty-six vancomycin courses from 18 eligible patients were identified between January 1, 2015 and February 6, 2017. After screening against exclusion criteria, 42 courses from 16 patients (mean age, 8 [SD, 6] years; mean dry weight, 26 [SD, 17] kg) were included (Fig. 1). The characteristics of the patients are summarized in Table 1. The majority of patients received IV vancomycin therapy for empiric treatment of HD/HDF-related infections (88%). The mean vancomycin dose was 10 mg/kg per dose infused over 1 hour (in 40 courses) or 2 hours (in 2 courses if patient has red man syndrome) for both initial and subsequent vancomycin doses. At baseline, almost all patients were febrile. The majority of courses (37 of 42, 88%) were discontinued after 48 hours of therapy, except for 5 courses with microbiologically documented HD/HDF-related infections (coagulase-negative *Staphylococcus* [n = 3], *Micrococcus luteus* [n = 1], and *Enterococcus* species [n = 1]) that required up to 10 days of vancomycin (median, 8.76 [interquartile range, 6.09–9.02] days). Eleven of 16 (69%) patients were on HD compared with 5 of 16 (31%) on HDF. All dialyzers were high flux. The URR and Kt/V values demonstrated that all courses had adequate dialysis sessions based on the Kidney Disease Outcomes Quality Initiative requirements of URR ≥ 65% and $Kt/V \geq 1.2$.[33]

Of the 42 courses, there were a total of 180 serum vancomycin concentrations (17 were below the limit of detection and were excluded from analyses). Nine courses from 6 patients with a complete set of detectable concentrations collected before, immediately after, 1 hour after, and 4 hours after dialysis were used in final model optimization. The mean serum vancomycin concentrations at each sampling timepoint after the first dose and after subsequent doses (i.e., second dose or later) (Supplementary Figures S1 and S2, respectively) showed a decline after dialysis, and then a rebound phase, which occurred 4 hours after the dialysis session ended.

Fifteen courses from 10 patients who had at least 2 detectable concentrations were used in the initial estimation of PK parameters (Table 2). The mean vancomycin removal was 56% (SD, 11%) during HD/HDF (n = 15) followed by a 23% (SD, 14%) rebound within 4 hours postdialysis (n = 10), thus the overall mean net drug removal was 43% (SD, 13%).

Table 1. Baseline characteristics of the study population

Number of courses per patient, n (%)	
1 course	5 (31.25)
2 courses	7 (43.75)
5 courses	3 (18.75)
8 courses	1 (6.25)
Male, n (%)[a]	7 (43.75)
Age, years, mean (SD)[a]	8.17 (5.55)
Infant (<1 year), n (%)	2 (12.5)
Toddler (1 to <3 years), n (%)	2 (12.5)
Preschool (3 to <6 years), n (%)	2 (12.5)
School age child (6 to <12 years), n (%)	6 (37.5)
Adolescent (12 to <18 years), n (%)	4 (25)
Dry weight, kg, mean (SD)[a]	26.08 (17.13)
Urine output, ml/kg per hour, mean (SD)[b]	1.06 (0.76) in 22 courses; no urine output in 20 courses
No urine output, n (%)[b]	20 (47.62)
Indication for vancomycin, n (%)[b]	
Empiric	37 (88.10)
Microbiologically documented infection	5 (11.90)
Initial vancomycin dose (mg/kg), mean (SD)[a]	10.50 (1.50)
Subsequent vancomycin doses (mg/kg), mean (SD)[a]	9.98 (0.39)
Other antibiotics given in combination with vancomycin, n (%)	Total = 38 (90.48)
Ceftazidime	1 (2.38)
Ceftriaxone	20 (47.62)
Piperacillin-tazobactam	2 (4.76)
Tobramycin	15 (35.71)
Type of dialysis, n (%)[a]	
HD	11 (68.75)
HDF	5 (31.25)
Prescribed number of dialysis sessions per week, n (%)[a]	
2 sessions	1 (6.25)
3 sessions	7 (43.75)
4 sessions	1 (6.25)
5 sessions	1 (6.25)
6 sessions	1 (6.25)
7 sessions	5 (31.25)
Prescribed duration per dialysis session, n (%)[a]	
2 h	3 (18.75)
3 h	10 (62.50)
4 h	3 (18.75)
Actual duration of dialysis session (after first vancomycin dose), mean (SD)[b]	2.95 (0.70)
Type of dialyzer used, n (%)[b]	
Polyflux 2H (Baxter Renal Care)	5 (11.90)
Xenium +H9 (Baxter Renal Care)	2 (4.76)
Xenium +H11 (Baxter Renal Care)	3 (7.14)
FX paed (Fresenius Medical Care)	2 (4.76)
FX40 (Fresenius Medical Care)	16 (38.10)
FX50 (Fresenius Medical Care)	7 (16.67)
FX60 (Fresenius Medical Care)	2 (4.76)
FX800 (Fresenius Medical Care)	5 (11.90)
Urea clearance, ml/kg per min, mean (SD)[b]	5.38 (1.34)
Dialysate flow rate, ml/min, mean (SD)[b]	311.54 (171.66)
URR, %, mean (SD)[b]	73.69 (7.24)
Kt/V, mean (SD)[b]	1.56 (0.33)

HD, hemodialysis; HDF, hemodiafiltration; IQR, interquartile range; *Kt/V*, *K* is dialyzer clearance of urea, *t* is dialysis time, *V* is volume of distribution of urea; SD, standard deviation; URR, urea reduction ratio.
[a]By patient.
[b]By course.

Table 2. Estimated pharmacokinetic parameters based on observed serum vancomycin concentrations from each vancomycin course

Parameter	Number of courses, n[a]	Mean (SD)	Median (IQR)
Percent drug removal	15	56.38 (10.74)	59.73 (55.86–62.38)
Percent drug rebound	10	22.97 (13.53)	21.78 (16.05–13.41)
Percent net drug removal	9	42.69 (12.62)	46.78 (43.10–52.39)
$k_{e,\text{intradialytic}}$ (h^{-1})	15	0.26 (0.10)	0.26 (0.19–0.32)
$t_{1/2,\text{interdialytic}}$ (h)	15	3.09 (1.30)	2.73 (2.17–3.73)
$Cl_{\text{intradialytic}}$ (L/kg per h)	7	0.36 (0.40)	0.20 (0.12–0.37)
$k_{e,\text{interdialytic}}$ (h^{-1})	10	0.020 (0.024)	0.013 (0.011–0.019)
$t_{1/2}$,interdialytic (h)	10	69.76 (57.34)	59.74 (38.04–69.62)
$Cl_{\text{interdialytic}}$ (L/kg per h)	9	0.013 (0.007)	0.012 (0.010–0.016)
V_d (L/kg)	9	0.80 (0.30)	0.84 (0.62–1.06)

$Cl_{\text{intradialytic}}$, clearance during dialysis; $Cl_{\text{interdialytic}}$, clearance while off dialysis; IQR, interquartile range; $k_{e,\text{intradialytic}}$, elimination constant during dialysis; $k_{e,\text{interdialytic}}$, elimination constant while off dialysis; SD, standard deviation; $t_{1/2}$,interdialytic, half-life while off dialysis; $t_{1/2,\text{interdialytic}}$, half-life during dialysis; V_d, volume of distribution.
[a]Number of vancomycin courses with available vancomycin concentrations to estimate pharmacokinetic parameters.

All detectable concentrations from the 42 courses were used in developing the 1- or 2-compartment models. The first-order, 1-compartment model demonstrated the best fit compared with the 2-compartment model (AIC of 14.4 vs. 27.3 and BIC of 11.1 vs. 23.2, respectively, for 1- and 2-compartment models). The mean V_d was 0.65 (SD, 0.19) L/kg, $k_{e,\text{intradialytic}}$ was 0.28 h^{-1} (SD, 0.11 h^{-1}), and $k_{e,\text{interdialytic}}$ was 0.0049 h^{-1} (SD, 0.004 h^{-1}).

Using the nonlinear least-square generalized reduced gradient optimization method, the fit of the 1-compartment model improved significantly for each of the 9 courses with a complete set of detectable vancomycin concentrations (Figure 2). The RSS was significantly reduced in the final model compared with the initial model ($P = 0.004$). Table 3 summarizes the final least-squares estimation of PK parameters of each course. The k_e values were significantly greater during the intradialytic period than the interdialytic period ($P < 0.0001$).

Efficacy and safety endpoints were also explored. Since there were only 5 documented bacterial infections, concurrent use of antibiotics and the majority of patients had a short 2- to 3-day course, an association between AUC/MIC and outcomes was not further investigated. There were declining trends in WBC count (mean change, −18.08%; SD, 36.86%) and temperature (mean change, −3.2%; SD, 2.4%) from baseline to the end of the vancomycin course. Three patients remained febrile due to Epstein-Barr virus, cytomegalovirus, and *Mycobacterium* infection, respectively. All documented bacterial infections showed eradication of the organism on repeat blood cultures. During a follow-up of 1.5 years, no recurrent bacterial infections were identified. No ototoxicity was observed. Only 1 patient had red man

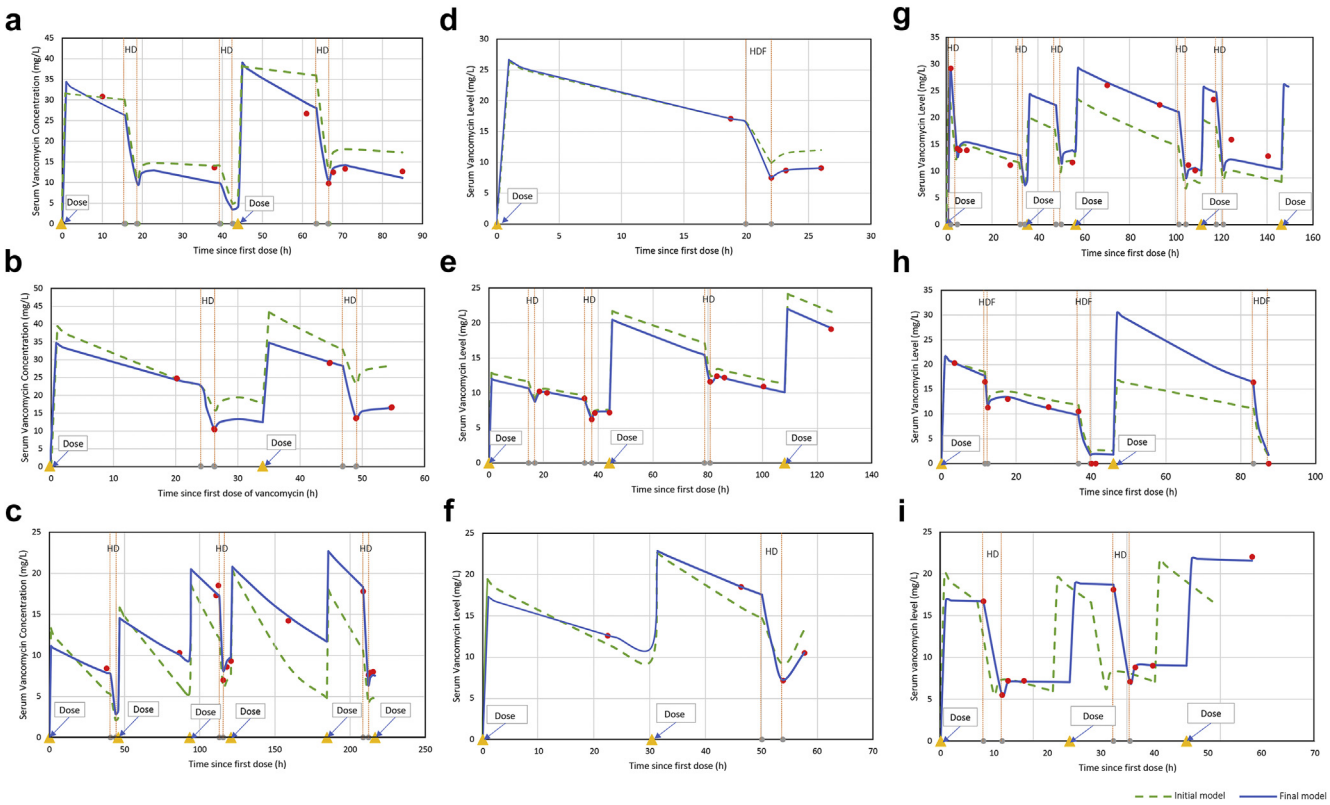

Figure 2. Individual serum vancomycin concentration-time plots for nine individual vancomycin courses with at least 4 serum vancomycin concentrations collected pre-, immediately-post-, 1-hour-post-, and 4-hour-post-dialysis (a–i). The final one-compartment pharmacokinetic model (blue line) was derived from optimization of elimination constants during intradialytic and interdialytic periods and volume of distribution using generalized reduced gradient method to minimize residual sum of squares from the initial model (dotted green line). Red circles represent observed serum vancomycin concentrations. Gray circles with orange dashed lines represent start and stop time of dialysis session. Yellow triangles represent doses given. HD, hemodialysis; HDF, hemodiafiltration.

syndrome, which was managed by infusing vancomycin for >2 hours and giving diphenhydramine when needed.

Based on linear regression analyses, we found statistically significant differences in PK parameters between types of dialysis (HD vs. HDF) and duration of dialysis session. HDF appeared to have a shorter $t_{1/2,\text{interdialytic}}$ (mean, 2.14 vs. 3.53 hours; $P = 0.04$) or greater $k_{e,\text{intradialytic}}$ (mean, 0.34 vs. 0.22 h^{-1}; $P = 0.04$) than HD (Table 4). The net drug removal was 50.9% in HDF and 38.6% in HD (Supplementary Table S1). No significant differences in baseline characteristics were evident between HD and HDF subgroups. Duration of the dialysis session appeared to have a positive trend with percent removal ($R^2 = 0.46$, $P = 0.005$) and net percent removal ($R^2 = 0.46$, $P = 0.046$) (Supplementary Figure S3). Longer duration of dialysis also appeared to have a trend with greater percent rebound, but was not statistically significant ($R^2 = 0.18$, $P = 0.23$). The $t_{1/2,\text{intradialytic}}$ was longest in patients who used Fx paed or Polyflux 2H compared with other dialyzers, but the analysis was limited by small sample size for each dialyzer type.

Tables 5 and 6 summarize the PTA for 24-hour AUC/MIC and 4-hour postdialysis concentrations from MCS after simulated loading and maintenance doses

Table 3. Pharmacokinetic model fitting for 9 vancomycin courses

Course	$RSS_{initial}$	RSS_{final}	$k_{e,\text{intradialytic,final}}$ (h^{-1})	$k_{e,\text{interdialytic,final}}$ (h^{-1})	$V_{d,final}$ (L/kg)
A	168.38	27.12	0.33	0.017	0.32
B	297.69	0.37	0.34	0.018	0.13
C	206.82	6.56	0.30	0.0092	0.89
D	21.82	3.8×10^{-8}	0.39	0.024	0.38
E	11.11	0.20	0.14	0.0083	0.79
F	19.30	2.7×10^{-8}	0.24	0.0014	0.84
G	87.95	36.68	0.28	0.0075	0.64
H	40.50	2.33	0.55	0.017	0.36
I	31.82	0.64	0.32	0.00010	0.86
Median (IQR)			0.32 (0.28–0.34)	0.014 (0.0083–0.017)	0.64 (0.38–0.84)

$k_{e,\text{intradialytic,final}}$, elimination constant during dialysis from final model; $k_{e,\text{interdialytic,final}}$, elimination constant when off dialysis from final model; RSS_{final}, residual sum of squares after using generalized reduced gradient nonlinear method to minimize RSS between the observed and predicted vancomycin concentrations; $RSS_{initial}$, residual sum of squares based on first-order, 1-compartment model before using GRG nonlinear method; $V_{d,final}$, volume of distribution from final model.

Table 4. Summary of influence of patient- and dialysis-related factors on vancomycin pharmacokinetic parameters

Factor	Effect on interdialytic PK parameters (off dialysis)	Effect on intradialytic PK parameters (on dialysis)
Sex	No significance	No significance
Age	↓ $t_{1/2}$ ($R^2 = 0.29$, $P = 0.13$)	No significance
Dry weight	No significance	No significance
Type of dialysis	No significance	Mean $t_{1/2}$ = 2.14 h (95% CI, 1.86–2.43) in HDF (n = 5) vs. 3.53 h (95% CI, 2.7–4.20) in HD (n = 10) ($P = 0.04$)[a]
Dialyzer model	No significance	Mean $t_{1/2}$ = 4.13 h (SD: 0.78) in Fx paed vs. 3.44 h (SD, 1.32) in Polyflux 2H vs. 2.05–2.76 h in other dialyzers
Frequency of HD/HDF sessions/week	Not comparable (limited data)	Not comparable (limited data)
Duration of dialysis session	No significance	↑% removal ($R^2 = 0.46$, $P = 0.0054$) ↑% net removal ($R^2 = 0.46$, $P = 0.046$)
Ultrafiltration rate	No significance	No significance
Dialysate flow rate	No significance	↑% removal ($R^2 = 0.14$, $P = 0.18$) ↑% rebound ($R^2 = 0.22$, $P = 0.17$)
Blood flow rate	No significance	↓ $t_{1/2}$ ($R^2 = 0.21$, $P = 0.087$)
URR	No significance	↓ $t_{1/2}$ ($R^2 = 0.24$, $P = 0.11$)
Kt/V	No significance	↓ $t_{1/2}$ ($R^2 = 0.21$, $P = 0.22$)
Urine output	↓ $t_{1/2}$ ($R^2 = 0.19$, $P = 0.28$)	No significance

↓, negative trend; ↑, positive trend; CI, confidence interval; *Cl*, clearance; HD, hemodialysis; HDF, hemodiafiltration; k_e, elimination constant; *Kt/V*, *K* is dialyzer clearance of urea, *t* is dialysis time, *V* is volume of distribution of urea; PK, pharmacokinetic; $t_{1/2}$, half-life; URR, urea reduction ratio; V, volume of distribution of urea.
[a]See Table S1 in Supplementary Material for more details.

postdialysis. Based on MCS, a loading dose of vancomycin 10 mg/kg per dose postdialysis was optimal to achieve PTA > 90% at 24-hour AUC/MIC ≥ 400 hours when MIC was 0.5 mg/L. This was considered appropriate for SickKids as a review of vancomycin susceptibilities showed the majority of isolated pathogens had an MIC ≤ 1 mg/L (Y Yau, e-mail correspondence, The Hospital for Sick Children, 2017).

To maximize PTA of a 4-hour postdialysis concentration within 5 to 12 mg/L for maintenance doses, 8 mg/kg per dose was optimal for daily dialysis sessions and 13 mg/kg per dose for 3 to 4 dialysis sessions per

Table 5. PTA (%) for 24-hour AUC/MIC ≥ 400 hours or 4-hour postdialysis vancomycin concentration with a daily dosing frequency (for daily dialysis sessions)

	24-hour AUC/MIC ≥ 400 h			4-hour postdialysis concentration	
Dose (mg/kg)	MIC 0.5 mg/L	MIC 1 mg/L	MIC 2 mg/L	Target 5–12 mg/L	Target 10–15 mg/L
After loading dose					
9	87.93	10.34	0.00	55.89	7.36
10	97.42	17.48	0.00	62.63	10.95
11	99.85	25.63	0.00	67.03	14.98
12	100	34.64	0.00	69.11	19.05
13	100	44.11	0.04	69.41	22.95
14	100	53.68	0.49	68.18	26.59
15	100	63.30	1.88	65.83	29.70
16	100	72.35	4.27	62.61	32.18
17	100	80.58	7.12	58.86	34.05
18	100	87.95	10.38	54.83	35.46
19	100	93.75	13.86	50.57	36.16
20	100	97.43	17.56	46.36	36.39
At steady state from maintenance dose					
6	89.03	23.97	0.97	47.80	12.95
7	96.36	35.72	2.04	51.75	16.50
8	99.22	47.82	3.83	53.38	19.87
9	99.91	59.58	6.40	52.60	22.02
10	100	69.99	9.90	50.75	24.06
11	100	78.71	14.34	48.01	25.32
12	100	86.14	19.54	44.76	25.92
13	100	91.52	25.19	41.14	26.33
14	100	95.27	31.25	37.49	26.10
15	100	97.63	37.44	33.88	25.71

AUC/MIC, area under the concentration–time curve over minimum inhibitory concentration; PTA, probability of target attainment.

Table 6. PTA (%) for 24-hour AUC/MIC ≥ 400 hours or 4-hour postdialysis vancomycin concentration after loading dose (every 2 days for 3 or 4 dialysis sessions per week)

	AUC/MIC ≥ 400 hours			4-hour postdialysis concentration	
Loading dose (mg/kg)	MIC 0.5 mg/L	MIC 1 mg/L	MIC 2 mg/L	Target 5–12 mg/L	Target 10–15 mg/L
After loading dose					
9	82.12	8.58	0.00	31.51	2.39
10	92.65	15.26	0.00	38.85	3.99
11	97.97	22.72	0.00	45.39	5.93
12	99.69	30.89	0.00	50.89	8.12
13	99.98	39.92	0.14	55.45	10.59
14	100	48.95	0.63	58.81	13.15
15	100	58.02	1.69	61.28	15.68
16	100	66.77	3.38	62.67	18.20
17	100	74.90	5.69	63.31	20.64
18	100	82.08	8.60	63.14	22.80
19	100	88.08	11.75	62.48	24.91
20	100	92.69	15.21	61.34	26.63
At steady state from maintenance dose					
6	71.23	11.22	0.29	27.95	4.82
7	84.79	19.38	0.65	34.61	6.90
8	93.41	29.28	1.31	40.35	9.08
9	97.75	39.78	2.42	44.73	11.49
10	99.45	50.25	4.09	48.32	13.80
11	99.91	60.29	6.40	50.47	15.94
12	99.99	69.39	9.43	51.61	17.97
13	100	77.28	13.21	52.02	19.80
14	100	83.88	17.46	51.75	21.24
15	100	89.02	22.21	50.86	22.62
16	100	93.15	27.95	49.53	23.49
17	100	95.81	33.27	48.06	24.39
18	100	97.65	38.60	46.23	25.01
19	100	98.76	43.95	44.31	25.29
20	100	99.41	49.34	42.20	25.59

AUC/MIC, area under the concentration–time curve over minimum inhibitory concentration; PTA, probability of target attainment.

week, but the difference in PTA compared with 10 mg/kg per dose was <5%. MCS results for the vancomycin dosing regimen of 10 mg/kg per dose postdialysis for 3-hour dialysis sessions every other day are illustrated in Figure 3. The mean vancomycin concentration–time profile simulated with this dosing regimen is depicted in Figure 4. Higher doses are needed for patients infected with vancomycin-sensitive pathogens with an MIC > 1 mg/L or for CNS infections targeting 10 to 15 mg/L for 4-hour postdialysis concentrations. The simulations suggested that patients would require >20 mg/kg per dose if infected with pathogens with an MIC of 2 mg/L to achieve PTA of 90% for 24-hour AUC/MIC ≥ 400 hours, but this led to 60% to 80% of 4-hour postdialysis concentrations of >15 mg/L.

DISCUSSION

This study is the first to characterize vancomycin PK parameters in a cohort of pediatric patients on HD and HDF and is the first to evaluate the vancomycin dosing strategy of 10 mg/kg per dose postdialysis while using TDM to guide redosing in such patients. Only one of the relevant pediatric case reports used a PK model to estimate vancomycin PK, but it had limitations that prevent application in current practice.[24] It established vancomycin PK in only a single 6-year-old patient and the dialysis sessions used a low-flux dialyzer (C-DAK 2500). Because of lack of information about vancomycin PK in pediatric patients on HD or HDF, optimal vancomycin dosing has remained unknown until now. Our study has provided PK parameter estimates using a population PK model to identify an optimal dosing regimen in this patient population.

The vancomycin concentration–time profiles indicate that the serum vancomycin concentrations declined after each HD/HDF session, with a mean drug removal of 56.4%. This finding is consistent with the case report by Bunchman et al., who found 67% drug removal in a 22-kg child and 50% in a 5.6-kg infant (ages not reported) using 3-hour HD sessions with a Baxter 550 dialysis machine and high-flux dialyzers.[22] Previous studies demonstrated a rebound phase after end of the dialysis session (i.e., vancomycin concentrations increased from immediately postdialysis to 4 hours postdialysis), which is likely due to re-equilibration between the central and peripheral compartments.[14,34,35] This pattern of drug removal and rebound in pediatric patients is similar to that in studies of adult patients being dialyzed by HD/HDF.[14] Furthermore, our mean net drug removal is similar to values reported in adult patients receiving HD/HDF on high-flux dialyzers (30%–55.1%).[36,37] However, our mean drug rebound is lower than what was described in studies on adult patients (36%–91%).[34,35] This is possibly due to the shorter distribution phase in pediatric patients compared with adults.[38]

The vancomycin concentration–time profile has been characterized as 1-, 2-, and 3-compartment PK models.[37,39,40] Wu et al. found that, although the 3-compartment model was most accurate and highly precise, the predictions using a 1-compartment model were less biased and preferable when limited blood samples were available for PK analysis.[39] Furthermore, a review by Marsot et al. demonstrated that, specifically in the pediatric population, a 1-compartment model was best for fitting the PK profile of the pediatric population.[41] Our study demonstrated that the first-order, 1-compartment model with least-squares algorithm provides good insight into the overall vancomycin concentration–time profiles of the 9 courses.

The least-squares estimate of $t_{1/2,\text{interdialytic}}$ from our study (median, 2.2 hours; interquartile range, 2.0–2.5 hours) is similar to the finding in the case report by Bunchman et al., who reported $t_{1/2,\text{interdialytic}}$ values of

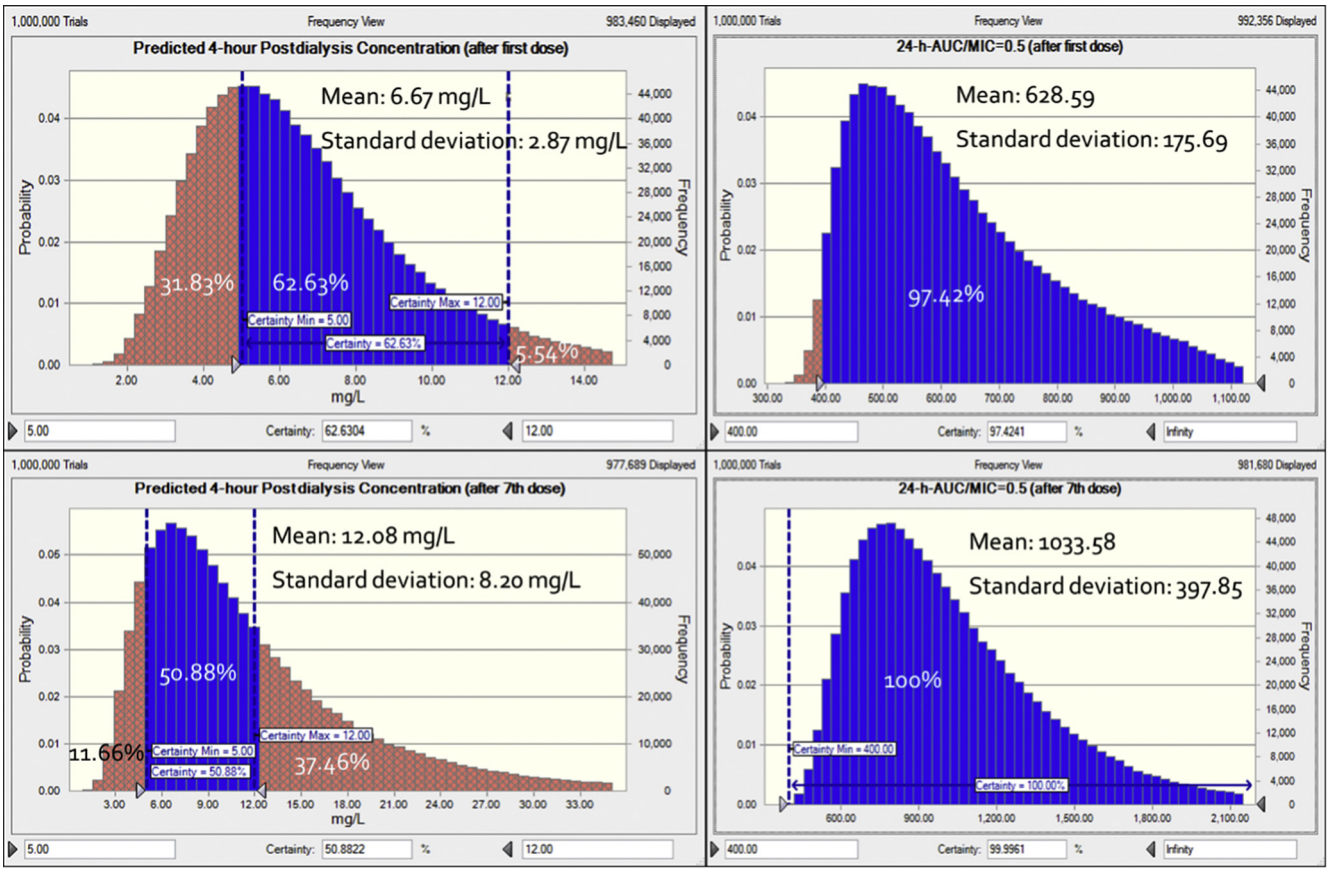

Figure 3. Probability distribution of predicted 4-hour post-dialysis concentration and 24-h area under the concentration-time curve to minimal inhibitory concentration ratio (AUC/MIC) for pathogens with MIC = 0.5 mg/L after first dose and at steady state (after seventh dose) from dosing regimen of 10 mg/kg/dose IV every 2 days for daily 3-hour dialysis sessions.

1.9 and 2.3 hours in 2 pediatric patients on HD with high-flux dialyzers.[22] They similarly demonstrated that $t_{1/2,\text{interdialytic}}$ was shorter than in studies that included patients using low-flux dialyzers, such as in the case of a 6-year-old child on 3-hour HD sessions with a cuprophane dialyzer that estimated $t_{1/2,\text{interdialytic}}$ to be 6 hours.[24]

Based on the literature review, dosing of vancomycin in adult patients typically calls for administering a loading dose followed by a maintenance dose, with subsequent dialysis sessions to maintain vancomycin serum trough concentrations between 15 and 20 mg/L.[42–52] However, this recommended therapeutic range is not supported by evidence from clinical trials and lower trough

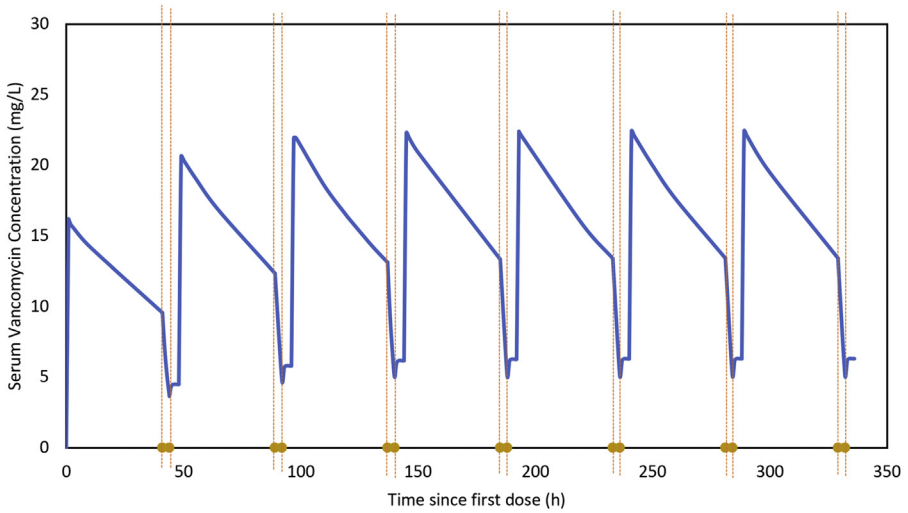

Figure 4. Final model of mean serum vancomycin concentration–time profile simulated with a vancomycin dosing regimen of 10 mg/kg/dose IV every 2 days (for 3 or 4 dialysis sessions per week). Orange dashed lines represent start and stop time for each dialysis session.

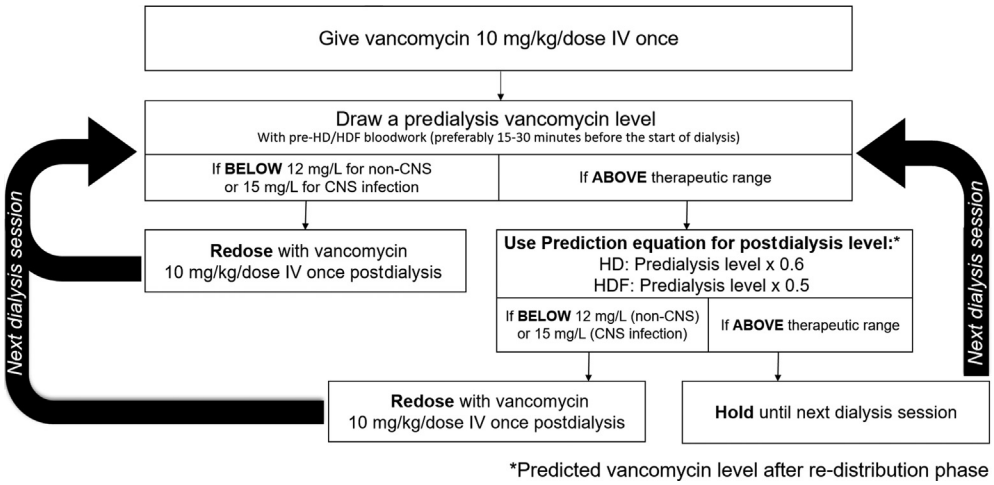

Figure 5. Vancomycin dosing and therapeutic drug monitoring guideline for pediatric patients receiving hemodialysis or hemodiafiltration. CNS, central nervous system; HD, hemodialysis; HDF, hemodiafiltration.

concentrations were associated with an AUC/MIC ≥ 400 hours.[13,17,18] Only a few studies in adults requiring HD/HDF assessed vancomycin dosing using the AUC/MIC target.[53,54] Because the majority of isolates identified at SickKids have a vancomycin MIC < 1 mg/L, vancomycin 10 mg/kg per dose was appropriate for the majority of pediatric patients.[55] Our MSC results suggest higher doses of >20 mg/kg/dose are needed to reach AUC/MIC ≥ 400 hours if pathogens have MIC > 1 mg/L, but may lead to overexposure in an HD/HDF population. Therefore, considerations of alternative antibiotics are needed.

A new dosing and TDM guideline for pediatric patients on HD/HDF was implemented at our hospital (Figure 5). We recommend collecting serum vancomycin concentrations predialysis rather than postdialysis to prevent delay in redosing or discharge from the dialysis clinic. Because the study showed the mean net drug removal was ~40% for HD and 50% for HDF for 3- to 4-hour dialysis sessions, the postdialysis concentration after the rebound phase was predicted by multiplying the predialysis concentration by 0.6 for HD and 0.5 for HDF, if the vancomycin concentration was above the therapeutic range to assess for redosing. The following were excluded from guideline use: the prediction equation for patients receiving HD/HDF for <2 hours or >4 hours; having inadequate dialysis sessions; Kt/V <1.2 and URR <1.5; and use of low-flux dialyzers, peritoneal dialysis, or continuous renal replacement therapy.

This study has several limitations. Data were collected retrospectively, resulting in missing vancomycin serum concentrations, which could increase uncertainty or variability in PK parameter estimations. About 17 of 180 (9%) vancomycin concentrations were excluded because they were below the limit of detection (<5 mg/L). Furthermore, due to vancomycin concentrations in dialysate solution below the assay's limit of detection, drug recovery and dialysis clearance could not be directly determined. The maximum vancomycin rebound was assumed to occur at 4 hours postdialysis; however, this study did not collect vancomycin concentrations beyond 4 hours to validate this, and the rebound effect may be underestimated. The present study suggests that duration and type of dialysis are both significant factors in vancomycin PK, yet this regression analysis was limited by the small sample size and was not powered to analyze this objective. Furthermore, a variety of dialyzers were used, made from different membrane materials and surface areas, so permeability and clearance of vancomycin could differ between types. Unfortunately, the sample size in each subgroup of dialyzer type was insufficient for comparison of PK parameters. Any clinically significant impact of these covariates requires a future investigation with a larger sample size. Furthermore, only 5 patients had documented infection, so the association of AUC/MIC or trough concentrations and efficacy and safety endpoints could not be investigated. Our dosing recommendations are based on an MIC value of <1 mg/L, and not generalizable for pathogens for higher MIC values.

In conclusion, HD and HDF appear to significantly remove vancomycin in pediatric patients, with rebound occurring at 4 hours postdialysis. Type and duration of dialysis may be important determinants of vancomycin PK in such patients. This study also generated hospital recommendations for vancomycin dosing and TDM guideline in HD/HDF patients and evaluated robustness using simulations. Based on MCS, an initial 10 mg/kg per dose postdialysis followed by TDM to assess redosing after subsequent dialysis

sessions was recommended. Future directions include external validation of the PK model and dosing in clinical practice as well as expanding sample size to assess the significant effects of covariates and their implications on the PK model.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Appendix. List of equations used to estimate pharmacokinetic parameters.

Figure S1. Serum vancomycin concentration after first dose of therapy. HD(F), hemodialysis or hemodiafiltration.

Figure S2. Serum vancomycin concentration after subsequent doses of therapy. HD(F), hemodialysis or hemodiafiltration.

Figure S3. Influence of duration of dialysis session on percent removal, percent rebound, and net percent removal of vancomycin.

Table S1. Pharmacokinetic parameters between hemodialysis and hemodiafiltration.

The Modified STROBE Statement.

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