Bon Secours Richmond
Memorial Regional Medical Center
Pharmacy & Therapeutics Committee
Evaluation of Vancomycin Dosing Protocol in Patients Receiving High-Flux Dialysis
1/2016

Background:
The current vancomycin dosing protocol for intermittent high-flux dialysis patients was approved by P&T and MEC. The protocol is based on previous published medical literature. Patients receive a 25 mg/kg loading dose and 500 mg at the end of each dialysis. Serum levels are drawn after the 1st maintenance, and the dose is adjusted with a goal trough level in the range of 15-20 mcg/ml.

Purpose of MUE:
To determine the success rate of this protocol by evaluating initial trough levels, adherence by pharmacy staff, and the possibility of need to change the protocol.

Endpoints:
- Primary endpoint: percentage of initial therapeutic vancomycin troughs
- Secondary endpoints: percentage of appropriately drawn troughs and appropriately dosed vancomycin loads

Methods:
- Retrospective chart review of patients receiving vancomycin from 11/29/13 to 08/23/15
- Study participants were identified using a pharmacokinetic dosing monitoring tool utilized by the pharmacy department to monitor patients
- Inclusion criteria: patients who were admitted as inpatient from November 2013 to August 2015, who received vancomycin while on intermittent high-flux dialysis at any point during their inpatient stay with at least one trough drawn.
    - Patients were included in the study more than once if they had multiple hospital stays during the study review period
- Exclusion criteria: patients receiving continuous renal replacement therapy, high-flux dialysis due to acute renal failure (ARF)
- De-identified data collected: demographics, duration of therapy, treatment diagnosis, loading dose, maintenance dose, administration times of all doses, and trough level and time of level
- Pharmacokinetic Model:
    - One compartment open model equations were used to calculate the predicted trough for each patient using the individual's dosing history and weight by the method of superposition. A non-linear fitting routine was used to minimize the sum of the square of the errors for all patients, sum of (actual level -predicted level)^2, to optimize the pharmacokinetic parameters ($Vd_{l/kg}$, $Cl_{l/hr\ dialysis}$, $Cl_{l/hr\ renal}$). Analysis assumes clearance is independent of patient weight. The following equations were used during the fittings.

      Sum of Square of Errors = $\sum_{1\ to\ n}$ (Actual Level – Predicted Level)^2

      Trough Predicted = $\sum_{1\ to\ n}$ Cp from loading doses + $\sum_{1\ to\ n}$ Cp from Maintenance doses

      Cp_{trough} Loading Dose = LD/Vd*Exp$^{(-((Clrenal/Vd)*Time\ to\ trough + (Cldialysis/Vd)*4\ hours*Number\ of\ Dialyses))}$

      Cp_{trough} Maintenance Dose = MD/Vd*Exp$^{(-((Clrenal/Vd)*Time\ to\ trough + (Cldialysis/Vd)*4*Number\ of\ Dialyses)}$

- Primary and secondary outcomes will be analyzed using descriptive statistics.
- Due to recent changes in dosing protocol the analysis was repeated to optimize the pharmacokinetic parameters ($Vd_{l/kg}$, $Cl_{l/hr/kg\ dialysis}$, $Cl_{l/hr/kg\ renal}$) to access the impact of assuming vancomycin clearance is related to patient weight.

Results [average (Standard Deviation)]:

- Number of Patients Reviewed: 52
- Age: 64 years old (SD: 12.1)
- Male: 70%
- Height: 66.8 inches (SD: 4.2)
- Weight: 83.5 kg (SD: 24.1)
- Body Surface Area: 1.9 (SD: 0.3)
- Length of therapy: 8.13 days (SD: 3.8)
- Indication:
    - Sepsis (29/52, 55.8%)
    - Pneumonia (11/52, 21.2%)
    - UTI (5/52, 9.6%)
- Loading Dose: 1735 mg (median: 1750 mg, SD: 506)
    - Loading Dose: 24.7 mg/kg (SD: 5.6)
    - Note: all LD were rounded to nearest 250 mg
- All MD were originally started at 500 mg
- Average number of MD administered before the first trough: 1.34 (SD: 0.84)
    - 36/52 (69.2%) patients had troughs drawn after the appropriate number of LDs
    - 3/52 (5.77%) patients did not receive a MD prior to a trough level being drawn
- Average time from LD to first MD: 2.26 days (Median 1.66, SD: 1.65)
- For those patients who received a MD prior to trough (94.2%):
    - Average time from MD to trough: 1.92 days (Median 1.73, SD: 0.63)
- Average trough level for ALL patients: 16.5 mcg/mL (Median 16.3, SD: 4.7)
- Average trough, Based on PK model: 16.3 mcg/mL (SD: 3.2)
- Measured Troughs
    - 10-20 mcg/mL: 41/52 (78.8%)
    - <10 mcg/mL: 1/52 (1.9%)
    - 10-<15 mcg/ml: 18/52 (34.6%)
    - 15-20 mcg/mL: 23/52 (44.2%)
    - >20 mcg/mL: 10/52 (19.2%)
- Kinetic Parameters derived after data fitting optimization
    - Clearance during dialysis: 6.9 liters/hour
    - Clearance renal: 0.3348 liters/hour
    - Volume of distribution: 1.17 liters/kg

- Analysis of Pharmacokinetic Model: The top model has the lowest SSE and best precision. The middle two models are included to show the impact of other volume of distributions which were set at a fixed value on data fittings. The last model demonstrates the impact of weight-based dosing.

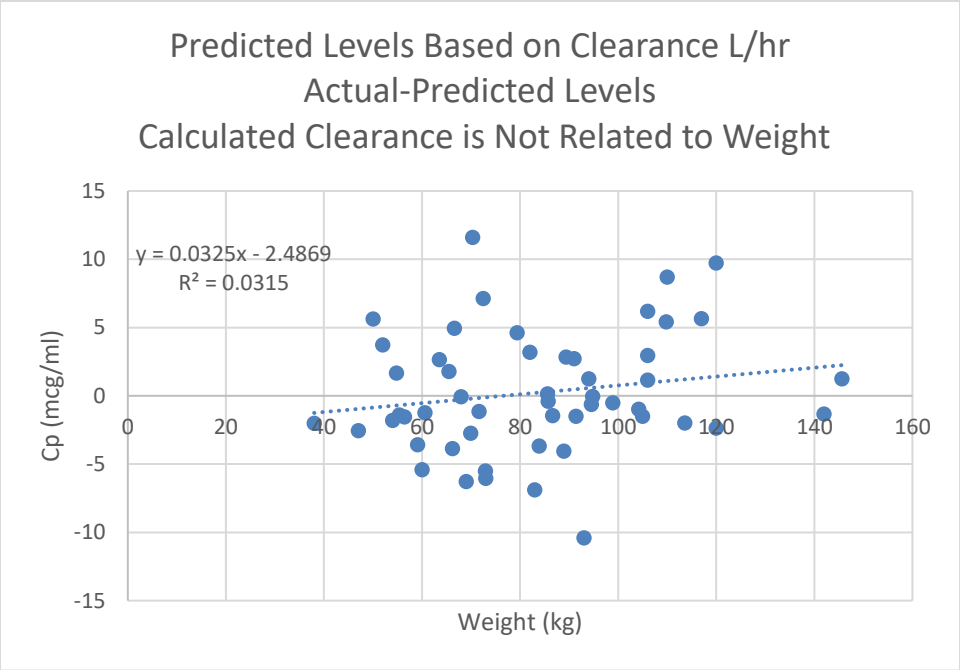
Optimized Parameters	Sum of Square of Errors (Predicted-Actual)^2	Bias (mg/dl)	Precision	Actual versus predicted trough means (SD)	Absolute (Actual-Predicted) <= 5	Absolute (Actual-Predicted) <= 7.5	Absolute (Actual-Predicted) <=10
Vd 1.17 l/kg, Cl_{renal} 0.3348 l/hr, Cldialysis 6.9 l/hr, AUC 750 mg (429)	**995**	**0.226**	**0.609**	**16.5(4.7) vrs 16.3(3.2)**	**73.1%**	**92.3**	**96.2**
Vd 0.9 l/kg, Cl_{renal} 0.343 l/hr, Cldialysis 6.72 l/hr, AUC 750 (433)	1264	-1.7	0.68	16.5(4.7) vrs 18.2(4)	71	88	98
Vd 0.65 l/kg, Cl_{renal} 0.536 l/hr, Cldialysis 5.57 l/hr, AUC 750mg (391)	1585	-0.024	0.77	16.5(4.7) vrs 16.5(5.4)	65	86.5	96.2
Vd 1.1 l/kg, Clrenal 0.0066 l/kg/hr, Cldialysis 0.04896 l/kg/hr	**1522**	**0.314**	**0.75**	**16.5 (4.7) Vrs 16.2 (3.8**	**61.5**	**84.6**	**94**

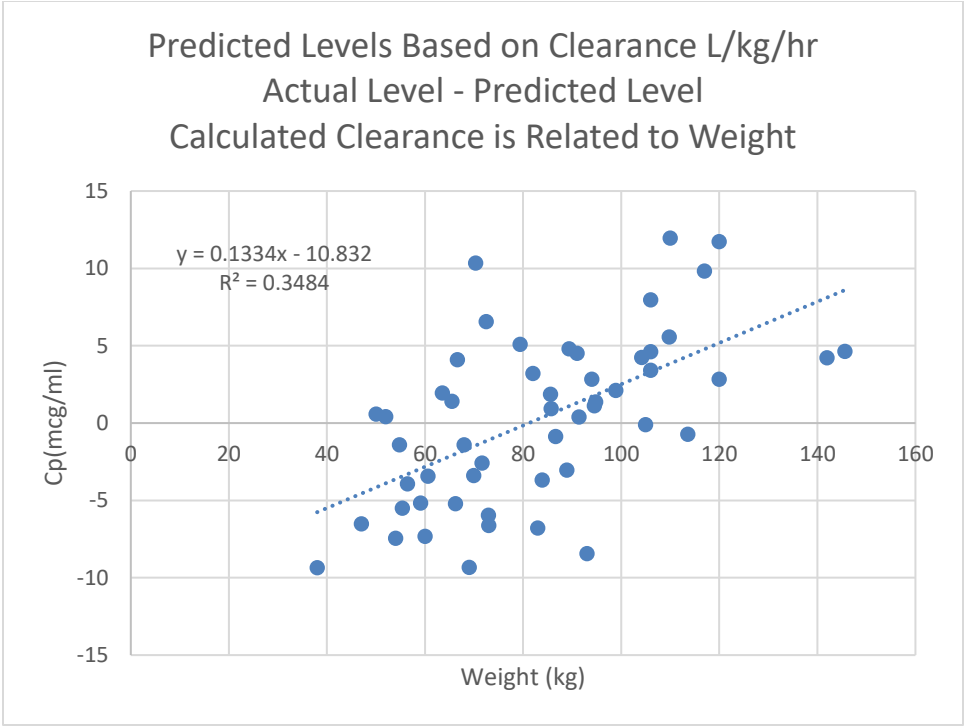
- Vancomycin Elimination
    - The body is cleared of amount equivalent to 40% of each dose during dialysis using the current protocol of giving the dose during the last hour of dialysis. An equivalent amount is cleared renally during the dosing interval. If the dose is given after dialysis the achieved levels are expected to be higher than noted above.
- Impact of patient's weight when using a set or standard dose in dialysis patients:
    - Peak: a higher weight gives a lower peak due to larger Vd
    - Trough: a higher weight gives higher trough as a larger Vd gives a lower elimination rate (K=Cl/Vd)
- AUC calculated
    - 500 mg maintenance dose during dialysis: 286
    - 750 mg maintenance dose during dialysis: 429

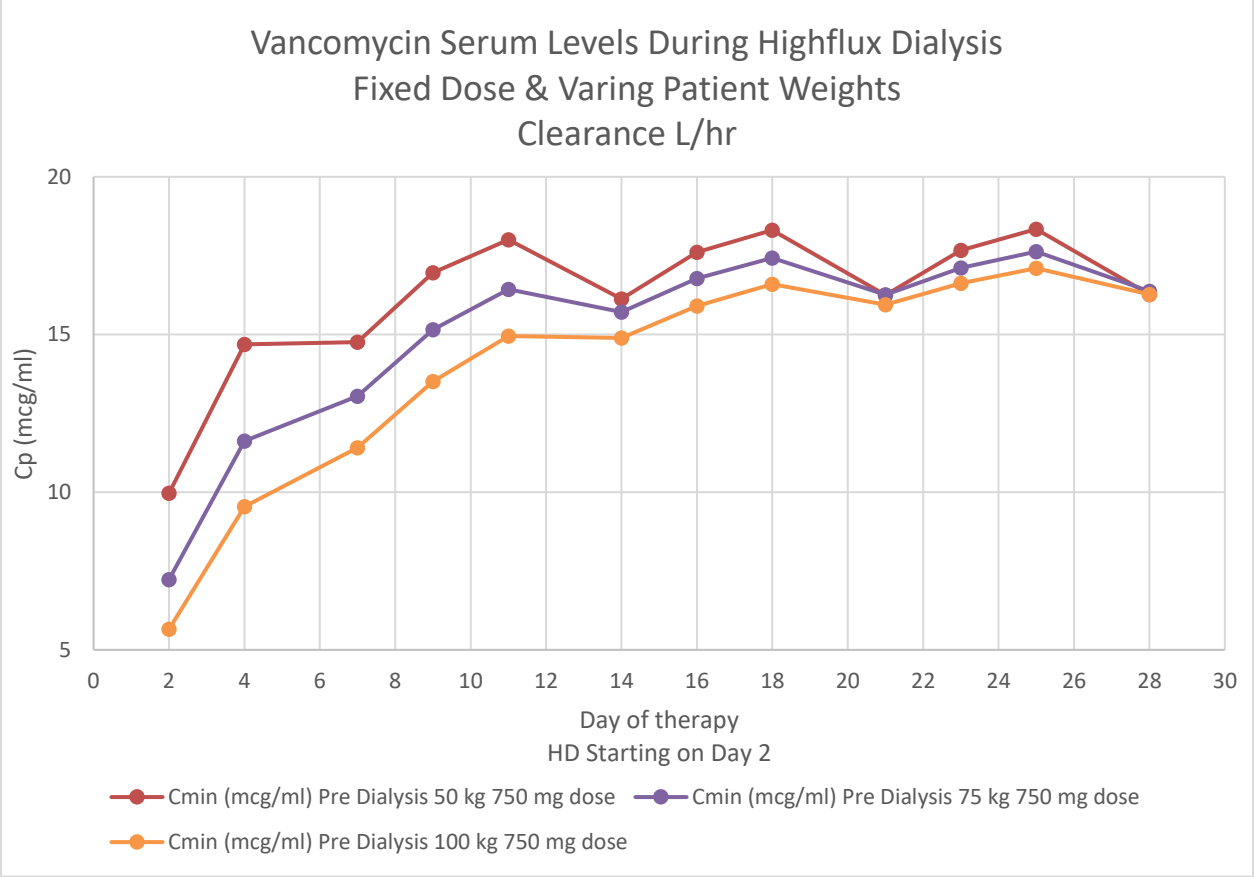
    - 1000 mg maintenance dose during dialysis: 572
- Patients requiring dosage adjustment: 29/52 (55.8%)
    - 16/29 (55%) had an adjustment
        - 11/13 (84.6%) of patient not receiving an adjustment had a reason for not adjusting.
        - 2 patients did not receive and adjustment when indicated, one patient's trough was just over 20.

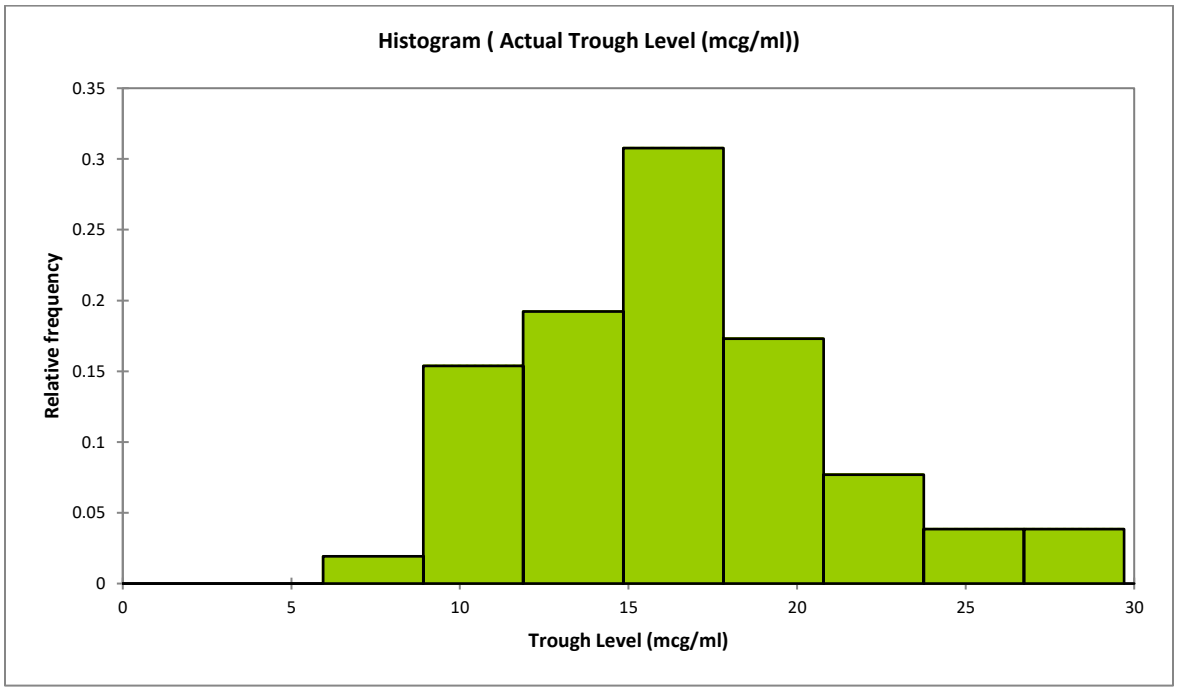
Conclusions & Recommendations:

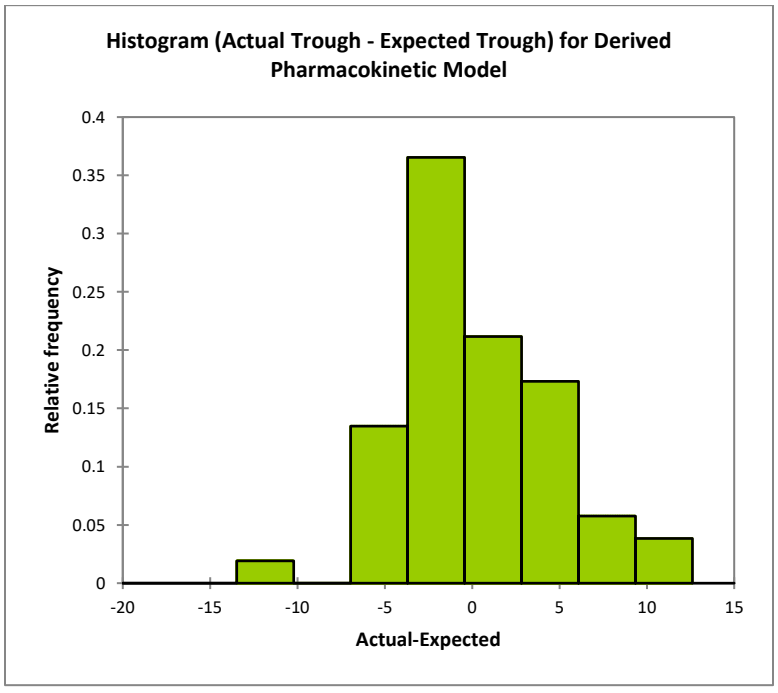
- An uncapped loading dose of 20-25 mg/kg is recommended. The current loading dose is achieving a peak of approximately 21 mcg/mL secondary to the patients expanded volume of distribution (1.17 l/kg) found in the analysis. The time to achieve levels near steady state is approximately 14 days without an loading dosing.
- A non-weight adjusted dose of 750 mg maintenance dose is recommended and will achieve an AUC of 429 mg/hour/liter per day.
- Weight based maintenance doses are not recommended as clearance is not related to body weight
- The current protocol, 500 mg at HD, is achieving lower than desired initial levels (15-20 mcg/mL) in 44.2% of patients.
- A follow up audit is recommended to valid protocol changes.




Predicted Levels Based on Clearance L/kg/hr
Actual Level - Predicted Level
Calculated Clearance is Related to Weight
y = 0.1334x - 10.832
R² = 0.3484
Cp(mcg/ml)
Weight (kg)
15
10
5
0
-5
-10
-15
0
20
40
60
80
100
120
140
160


Vancomycin Serum Levels During Highflux Dialysis
Fixed Dose & Varing Patient Weights
Clearance L/hr
Cp (mcg/ml)
Day of therapy
HD Starting on Day 2
Cmin (mcg/ml) Pre Dialysis 50 kg 750 mg dose
Cmin (mcg/ml) Pre Dialysis 75 kg 750 mg dose
Cmin (mcg/ml) Pre Dialysis 100 kg 750 mg dose
20
15
10
5
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30


Histogram (Actual Trough Level (mcg/ml))
Relative frequency
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
5
10
15
20
25
30
Trough Level (mcg/ml)


Histogram (Actual Trough - Expected Trough) for Derived Pharmacokinetic Model
Relative frequency
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-20
-15
-10
-5
0
5
10
15
Actual-Expected

Background:

Vancomycin has historically been used as the staple in empirical treatment for methicillin-resistant *Staphylococcus aureus* (MRSA)[1]. Patients who are at an increased risk for MRSA infections include patients with intravenous (IV) lines or catheters, patients who have been recently hospitalized, and patients whom reside in a long term care facility. Patients with end stage renal disease (ESRD) often fall into one or more of these categories[2].

Infection is the second leading cause of death in hemodialysis patients[3,4]. Approximately 75% of these mortalities related to bacteremia infections. In hemodialysis patients, *S. aureus* is the lead pathogen and accounts for approximately 25-30% of infections[3]. Based on these statistics, it is crucial to develop a success strategy in order to appropriately dose and treat.

Multiple strategies exist for vancomycin dosing in patients receiving high-flux dialysis; however specific dosing guidelines are not available. Additionally, there has been a recent change to target trough levels. Previous data supported a pre-dialysis vancomycin concentration between 5-20 mcg/mL. Recent guidelines increased the recommended pre-dialysis level to 15-20 ug/ml for health care associated infections, bacteremia and osteomyelitis[1].

Currently, very few studies have been conducted to analyze vancomycin dosing in intermittent dialysis patients. Additionally, these studies also have very small sample sizes. Some concerns in dosing vancomycin in patients on hemodialysis can be illustrated through the pharmacokinetic and pharmacodynamics behavior of vancomycin in different patient populations. These properties are compared in the table below[3].

	Normal Renal Function	Renal Disease
Clearance	80-90% unchanged via kidneys	
Half-Life	6-12 hours	100-200 hours in anuric patients
Vd (may be slightly higher in obese patients)	0.4-1 L/kg	0.72-0.9 L/kg in ESRD
Protein Binding	50-55%	20% in ESRD

Previous Studies:

- [1] Soto Guerrero Y1, Hernández Castillo R, Santiago E, et al. Evaluation of a vancomycin dosing regimen for patients on high flux hemodialysis: an observational study. *Bol Asoc Med P R.* 2012 Jul-Sep;104(3):10-4.
    - Purpose: to determine if the 1 gram LD before HFHD and 500 mg MD achieved a pre-dialysis concentration between 15-20 mcg/mL and to predict an adequate vancomycin dosage to achieve the new recommended levels
    - Reviewed 21 patients whom all adhered to the protocol. Each patient received 3 troughs drawn.
    - Results/Recommendations: The mean pre-dialysis concentration #1 was 10.8 mcg/mL, #2 was 13 mcg/mL, and #3 was 12 mcg/mL. Only 36% of HFHD sessions achieved an adequate vancomycin level. A liner regression analysis predicted that a 23 mg/kg LD and 8 mg/kg MD achieved the recommended pre-dialysis vancomycin concentration
- [2]Pai, AB and Pai MP. Optimizing antimicrobial therapy for gram-positive bloodstream infections in patients on hemodialysis. Adv Chronic Kidney Dis. 2006 Jul;13(3):259-70.
- [3]Vandecasteele SJ and De Vriese AS. Vancomycin dosing in patients on intermittent hemodialysis. *Semin Dial.* 2011;24:50-55.
    - Recommendations (based on previous studies):

TABLE 2. Proposed dose guidance for vancomycin in hemodialysis patients

Vancomycin dosing in hemodialysis patients	
Monitoring	Trough-level monitoring before each dialysis session
Target trough levels	15–20 μg/ml > 20 μg/ml: incremental risk for nephro- and ototoxicity < 15 μg/ml: incremental risk for treatment failure and resistance
Infusion rate	15 mg/minute, with end of infusion at the end of dialysis session
Loading dose	20–25 mg/kg actual (dry) body weight
Maintenance dose	No good data; fixed doses are inappropriate Probably guided by trough levels, interdialytic elapse, actual body weight, residual renal function
Maximal dose	4 g, also in extreme obesity
Timing of administration	Intradialytic administration is more convenient than postdialytic administration, dose is 13–34% higher than with post-HD dosing

- [4]Jeremiah CJ, Wills C, Bayly A, et al. Vancomycin dosing nomogram for haemodialysis patients. *Nephrology*. 2014;19:513-514.
    - 2011 audit at specific institution in Australia revealed that when patients received > 2 grams of vancomycin, only 14/38 demonstrated troughs 15-20 mcg/mL.
    - No previous nomogram was used (physician-driven dosing)

Table 1 Vancomycin dosing recommendations

Vancomycin level (mg/L)	Next vancomycin dose (mg)
<5	2000
5–15	1500
15–20	1000
20–25	500
>25	0

The initial dose of vancomycin should be a weight-based loading dose of 25 mg/kg (maximum 2 g). Levels should be done urgently at the commencement of the next dialysis session to guide further dosing, which should be calculated according to the table, and prescribed on the haemodialysis vancomycin medication order (maximum administration rate 1 g/h).

    - Following new nomogram, an additional audit was conducted
        - 25 patients receiving 28 courses of vancomycin
        - Median duration of therapy: 17 days
        - Most common indication: SSTI (32%)
        - Median duration to HD following vancomycin initial dosing was 1.8 days
        - Only 6/25 patients received 25 mg/kg LD; all others receiving 1 gram LD
        - Mean MD was 935 mg and followed the nomogram in 97% of cases
        - Troughs of 15-20 mcg/mL were obtained in 54.5 % of cases, 15% < 15 mcg/mL, and 4.2% >25 mcg/mL
- [5]Ariano RE, Fine A, Sitar DS, et al. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. *Am J Kidney Dis*. 2005 Oct;46(4):681-7.
    - 1 gram IV load during the last hour of dialysis session then 500 mg with every subsequent session predict troughs 5-20 mcg/mL
    - Sample of 22 patients, predialysis concentration range of 5- 20 mcg/mL was achieve in 96% of cases, 86% of levels between 5-15 mcg/mL