Bon Secours Richmond
Memorial Regional Medical Center
Pharmacy & Therapeutics Committee
Evaluation of Vancomycin Post HD Dosing Protocol in Patients Receiving High-Flux Dialysis
9/2020

Background:
The current vancomycin dosing protocol for intermittent high-flux dialysis patients was approved by P&T and MEC. The protocol caps the loading dose at 2000 mg (20 mg/kg) and employs an initial maintenance dose based on patient weight (500 mg for < 75 kg, 750 mg for 75 kg to less than 100 kg, 1000 mg for >= 100 kg) with doses being given after HD is complete. Serum levels are drawn after the first or second maintenance, and the dose is adjusted with a goal pre-dialysis level in the range of 15-20 mcg/ml or 20-25 mcg/ml depending on indication and with a goal AUC of 400-600 mcg/ml/24 hours. Efficacy is associated with the AUC. The AUC is related to the post dose peak, pre-dialysis level and the renal elimination rate between the levels. The contribution to the AUC from the time of the pre-dialysis level to the post dialysis pre dose level is negligible when the length of time from HD to the next dose is minimized. Vancomycin levels rebound post dialysis with equilibrium being achieved approximately 6 hours post dialysis with a range of up to 12 hours.

Purpose of MUE:
To determine the success rate of this protocol by evaluating vancomycin pre dialysis serum levels during therapy and to update the protocol if needed.

Endpoints:
- Primary endpoint: percentage of vancomycin levels within the goal ranges.
- Secondary endpoints: define the relationship of patient weight to dose required in mg and mg/kg.

Methods:
- Retrospective chart review of patients receiving vancomycin after the recent implementation of post dialysis vancomycin dosing.
- Study participants were identified using a pharmacokinetic dosing monitoring tool utilized by the pharmacy department to monitor patients.
- Inclusion criteria: chronic dialysis patients who were admitted as inpatient from 10/19/19 to 6/25/20, who received vancomycin while on intermittent high-flux dialysis at any point during their inpatient stay with at least one vancomycin level 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 and high-flux dialysis due to acute renal failure (ARF).
- De-identified data collected: demographics, duration of therapy, treatment diagnosis, loading dose, maintenance doses, administration times of all doses, hemodialysis dates and length of dialysis sessions, and vancomycin levels and time of levels.
- Pharmacokinetic Model:
    - An open one compartment linear model incorporating bolus equations was used to calculate the predicted pre-dialysis level(s) for each patient using the individual's dosing and dialysis history, length of each dialysis session and body weight by the method of superposition. A non-linear fitting routine was used to minimize the sum of the square of the errors for each patient and for all patients as a group, sum of (actual level - predicted level)^2, to optimize the population pharmacokinetic parameters (volume of distribution ($Vd_{L/kg}$), Clearance ($Cl_{L/hour\ dialysis}$), and Clearance ($Cl_{L/hour\ renal}$). The following equations were used during the fittings.

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

Level Predicted = $\sum_{1 \text{ to } n}$ Cp from loading doses + $\sum_{1 \text{ to } n}$ Cp from all Maintenance doses + Cp from initial level

Cp from Initial Level = Cp initial * $\exp^{(-((Clrenal/Vd)*Time\ to\ level) + (Cldialysis/Vd) * length\ of\ dialysis\ hours * Number\ of\ Dialysis\ sessions))}$

Cp from Loading Dose = LD/Vd * $\exp^{(-((Clrenal/Vd)*Time\ to\ level\ ) + (Cldialysis/Vd) * length\ of\ dialysis\ hours * Number\ of\ Dialysis\ sessions))}$

Cp from Maintenance Dose = MD/Vd * $\exp^{(-((Clrenal/Vd)*Time\ to\ level + (Cldialysis/Vd) * Length\ of\ Dialysis * Number\ of\ Dialysis\ sessions))}$

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

Root Mean Square Error = (SSE/n)$^{\wedge 0.5}$

Bias = $\sum_{1 \text{ to } n}$ (Actual Level – Predicted Level)/n

- Primary and secondary outcomes will be analyzed using descriptive statistics.

Results [average (Standard Deviation or actual range)]:

- Number of Patients Reviewed: 44
- Age: 65.8 years old (SD: 13.5)
- Male: 53.3%
- Height: 66.4 inches (SD: 4.2)
- Weight: 84.1 kg (SD: 22.1)
- Body Surface Area: 1.9 (SD: 0.26)
- Dialysis Length hours: 3.3 (0.48)
- Length of Observation: 3.7 days (Minimum 1, Maximum 15.4)
- Levels obtained by Indication Goal:
    - Indications with goal level 20-25 mcg/ml: 21.3 mcg/ml (SD 3.3) with an average dose of 774 mg
        - Average level within goal range: 55% (16/29)
            - Average level above goal range: 14% (4/29)
            - Average level below goal range: 31% (9/29)
    - Indications with goal level 15-20 mcg/ml: 19.3 mcg/ml (SD 4.4) with an average dose of 738 mg
        - Average level within goal range: 60% (9/15)
            - Average level above goal range: 27% (4/15)
            - Average level below goal range: 13% (2/15)
- Loading Dose: 1656 mg (SD: 338), 40 loading doses
    - Loading Dose: 19.8 mg/kg (SD: 3.3)
    - Seven patients had a post loading dose level drawn before the 1st HD
        - Average Post Loading Dose Level: 16.5 mcg/ml (SD: 3.3) (range 11-20.6 mcg/ml) with an average LD of 19.3 mg/kg
- Average Post HD Maintenance Dose (mg): 757 mg (9 mg/kg) for 134 doses
    - Maintenance Dose 1: 837 mg (500-2000 mg) 42 doses
    - Maintenance Dose 2: 716 mg (0-1000 mg) 37 doses
    - Maintenance Dose 3: 769 mg (500-1250 mg) 26 doses

    - Maintenance Dose 4: 683 mg (250-1000 mg) 15 doses
    - Maintenance Dose 5: 687 mg (500-1000 mg) 9 doses
    - Maintenance Dose 6: 800 mg (250 -1250 mg) 5 doses
- Average pre-HD level during maintenance doses for all patients: 20.9 mcg/mL (SD: 4.5)
    - Pre-HD-Maintenance Dose 1: 16.3 mcg/ml (Min: 11.1, Max 20.6)
    - Pre-HD-Maintenance Dose 2: 20.4 mcg/ml (Min 14.3, Max 31.2)
    - Pre-HD-Maintenance Dose 3: 21.5 mcg/ml (Min 13.2, Max 29.6)
    - Pre-HD-Maintenance Dose 4: 23.3 mcg/ml (Min 14.2, Max 29.5)
    - Pre-HD-Maintenance Dose 5: 21.2 mcg/ml (Min 16.5, Max 27.3)
    - Pre-HD-Maintenance Dose 6: 23.1 mcg/ml (Min 20.7, Max 26.3)
    - Pre-HD-Maintenance Dose 7: 23.1 mcg/ml (Min 17.2, Max 29.6)
- Average trough, based on population PK model: 19.6 mcg/mL (SD: 3.57)
- Measured Pre-HD Levels: 85 levels
    - 10 to <15 mcg/mL: 7/85 (8.2%)
    - 15 to 20 mcg/mL: 29/85 (34.1%)
    - > 20 to 25 mcg/ml: 35/85 (41.2%)
    - > 25 mcg/mL: 14/85 (16.5%)
- Dose (mg) required to obtain a Pre-HD Level of 20 mcg/ml based on individual kinetic parameters: 785 mg (SD: 240) (range 410-1398)
    - <= 500 mg: 2% (1/44)
    - > 500 - <=750 mg: 52% (23/44)
    - > 750 - <1000 mg: 30% (13/44)
    - >= 1000 mg: 16% (7/44)
- Population Kinetic Parameters derived from data fitting optimization
    - Vancomycin <u>dosed during HD</u> (prior MUE analysis)
        - Clearance during dialysis: 6.9 liters/hour
        - Clearance renal: 0.3348 liters/hour
        - Volume of distribution: 1.17 liters/kg
    - Vancomycin <u>dosed after HD</u> (current MUE analysis)
        - Clearance during dialysis: 4.08 liter/hour
        - Clearance renal: 0.4621 liters/hour
        - Volume of distribution: 1.03 liters/kg

- Analysis of Pharmacokinetic Model:

Optimized Parameters	Sum of Square of Errors (Predicted-Actual)^2	Bias (mcg/ml)	Precision RMSE (mcg/ml)	Actual versus predicted trough means (SD)	Absolute (Actual-Predicted) <= 2.5	Absolute (Actual-Predicted) <= 5	Absolute (Actual-Predicted) <= 7.5
Vd 1.03 L/kg Cl renal 0.4621 L/hour, Cl dialysis 4.08 L/hour	2022	-1.41	4.85	20.99 (4.5) versus 19.6 (3.6)	40%	71.8%	87%

- Vancomycin Elimination with Post HD Dosing
    - On average the body is cleared of amount equivalent to 33% of the post HD dose during dialysis. Approximately 67% is cleared renally during the dosing interval.

Overview of literature:

Most studies were single dose studies with small sample sizes, had a target range of 15-20 mcg/ml and vancomycin was administered during HD. Vancomycin has higher extraction when infused during high-flux HD then when given post HD. Extraction increases with longer infusions during dialysis and doses are usually increased 30-50% for 1- and 2-hour intra HD infusions. Administration of vancomycin after dialysis gives more consistent serum levels but requires more time in the dialysis suite. Two studies utilized post dialysis dosing. Barth 1996, studied 89 patients administered a loading dose of 20 mg/kg and a fixed maintenance dose of 500 mg post high flux dialysis with a target range of 10-20 mcg/ml. The average weight has 70.3 kg (SD 14.3 kg) with a mean duration of therapy was 11 days (3-54 days). Four hundred thirty-one (431) pre-dialysis level were analyzed. The mean pre-HD level was 15.9 mcg/ml with 60.6% in the target range, 13% were less than 10 mcg/ml and 5% were above 25 mcg/ml. No analysis of serum levels versus patient weight was performed. Maxon 2016, studied 21 patients, average weight 85 kg (SD 25 kg). Patients were administered a weight-based maintenance dose (500 mg for < 75 kg, 750 mg for 75-104.9 mg, 1000 mg for 105-129.9 mg, 1250 mg for > 130 kg) post dialysis while receiving high flux dialysis using an Optiflux F160NR membrane. As the dose was increased for heavier patients the percentage of patients in the desired therapeutic range of 15-20 mcg/ml fell (57%, 29%, 17%, to 0%) and the percent above the goal range increased (19%, 52%, 67%, to 100%). The percentage of patients outside of goal range was higher than the percent within range for all groups except for patients weighing less than 75 kg.

Current 2020 guidelines from IDSA, ASHSP, EIDS and SIDP recommend:

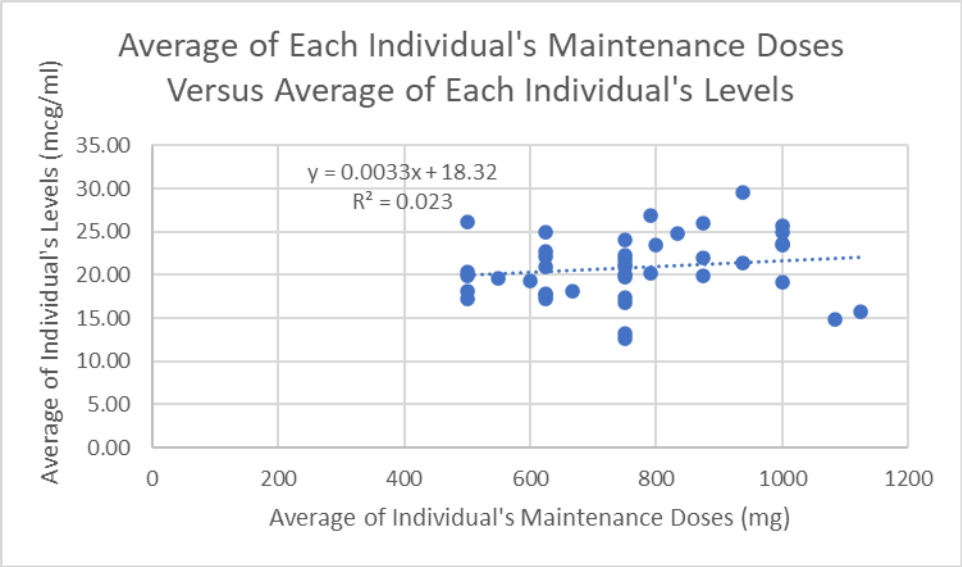
- Loading dose for high flux dialyzer: 25 mg/kg if not administered during dialysis or 35 mg/kg if administered during dialysis, based on totally body weight, capped at 3000 mg for patients who are critically ill, HD or RRT.
- Maintenance dose for high flux dialyzer: 10 mg/kg if administered after dialysis, 10-15 mg/kg if during dialysis
- Goal level: 15-20 mcg/ml pre-HD, and an AUC 400-600 mcg/ml/24 hours

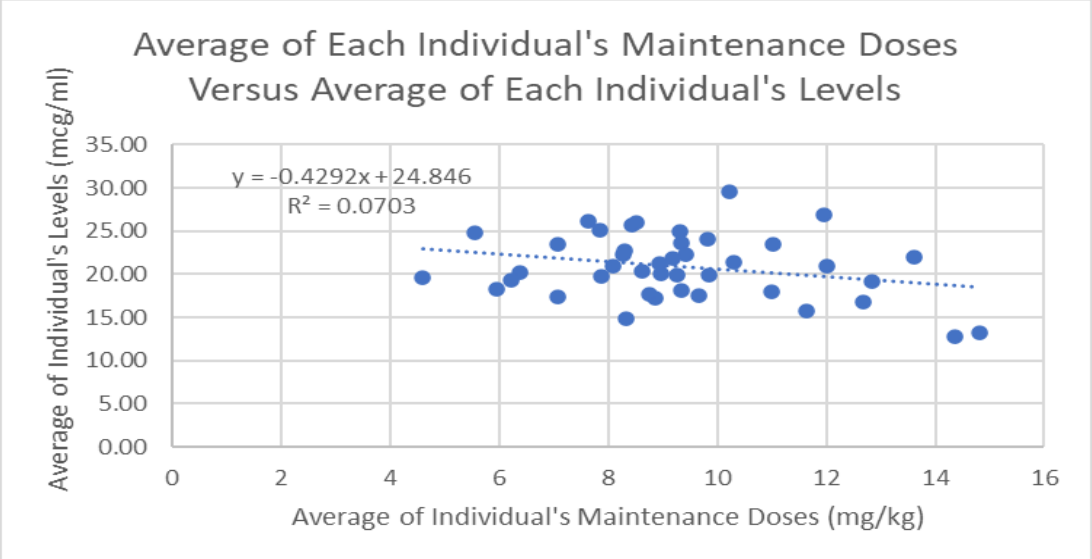
Conclusions & Recommendations:

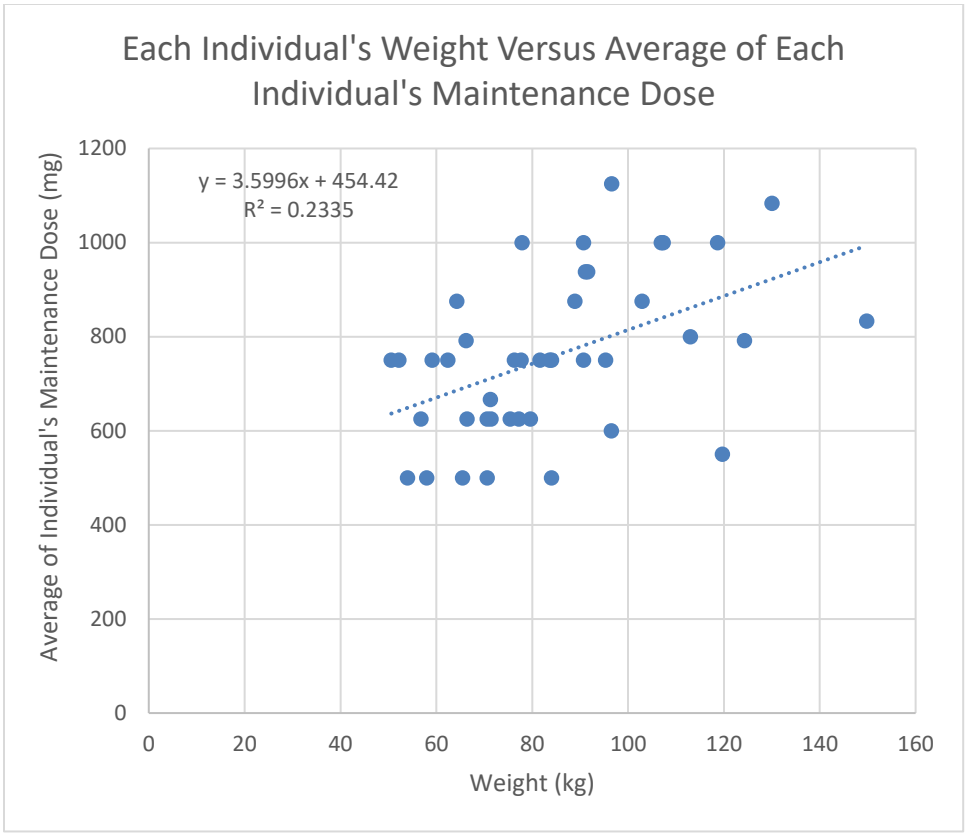
- Goal troughs of 15-20 mcg/ml are recommended as the expected AUCs are 400-600 mcg/ml/24 hours.
- A loading dose of 25 mg/kg is recommended with a dosage cap at 3000 mg as levels are lower than desired with the current protocol. The current protocol loading dose, 20 mg/kg, capped at 2000 mg, is achieving average levels before the first HD session of 16.5 mcg/ml (SD: 1.47) (range 11-20.6 mcg/ml) with an average dose of 19.3 mg/kg being given. Current guidelines recommend 25 mg/kg in serious infections as noted above.
- Our patients required a wide range of post HD maintenance doses, both in milligrams per dose (500-1125 mg) and mg/kg per dose (5-15 mg/kg), to maintain adequate serum levels. A very weak correlation between maintenance dose in milligrams or mg/kg and serum levels was found, possibly due to large variances in HD and renal vancomycin clearances. <u>The analysis does not support selection of maintenance dose based on patient weight in kg or by doses in mg/kg. The average dose to obtain a serum level of 20 mcg/ml was 785 mg.</u>
- A standard initial maintenance dose of 750 mg is recommended and is close to the average dose required for 20 mcg/ml.
- Periodic serum levels with dosing adjustments are suggested to guide dosing to maintain levels in the desired range (before the 2nd, 3rd, and 4th maintenance doses).
- Dosage adjustment of 250 mg to 500 mg are recommended when pre-HD levels are outside of the therapeutic range.
    - Goal 15-20 mcg/ml
        - Pre-HD level 10 to < 15 mcg/ml: increase prior dose by up to 250 mg
        - Pre-HD level >= 15 to <= 20 mcg/ml: no change

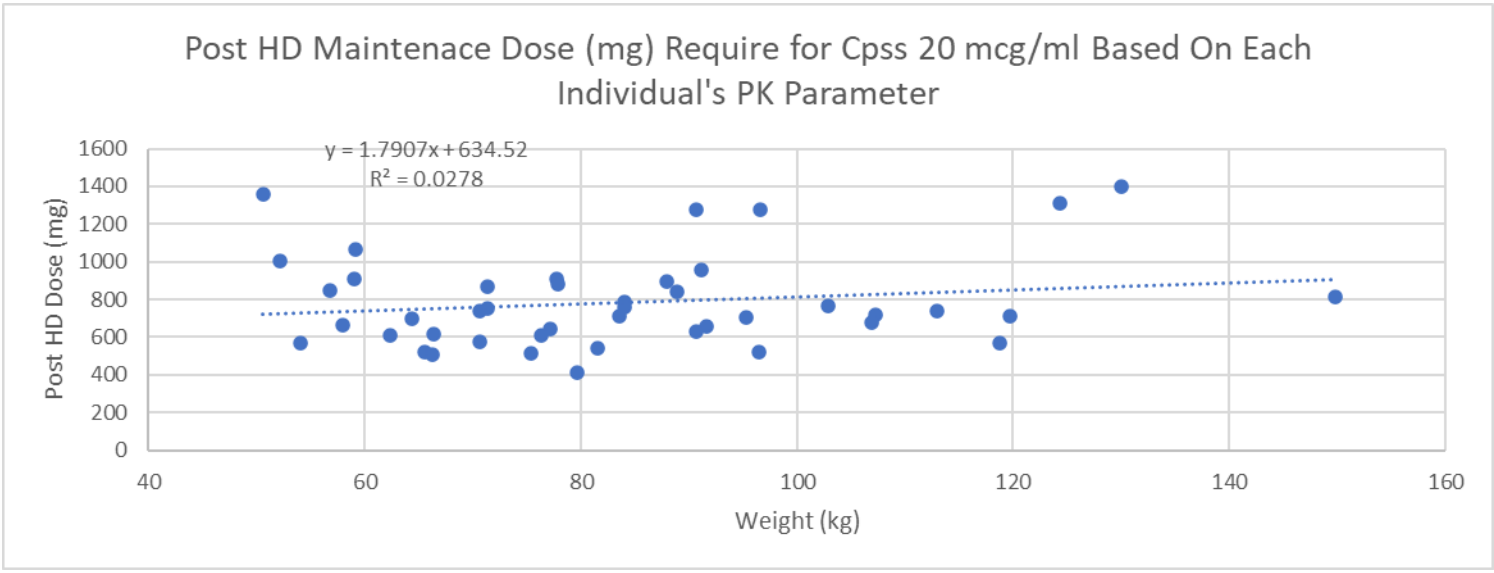
- Pre-HD level >= 25 to 30 mcg/ml: decrease dose by 250 to 500 mg, hold post HD dose if level > 25 mcg/ml

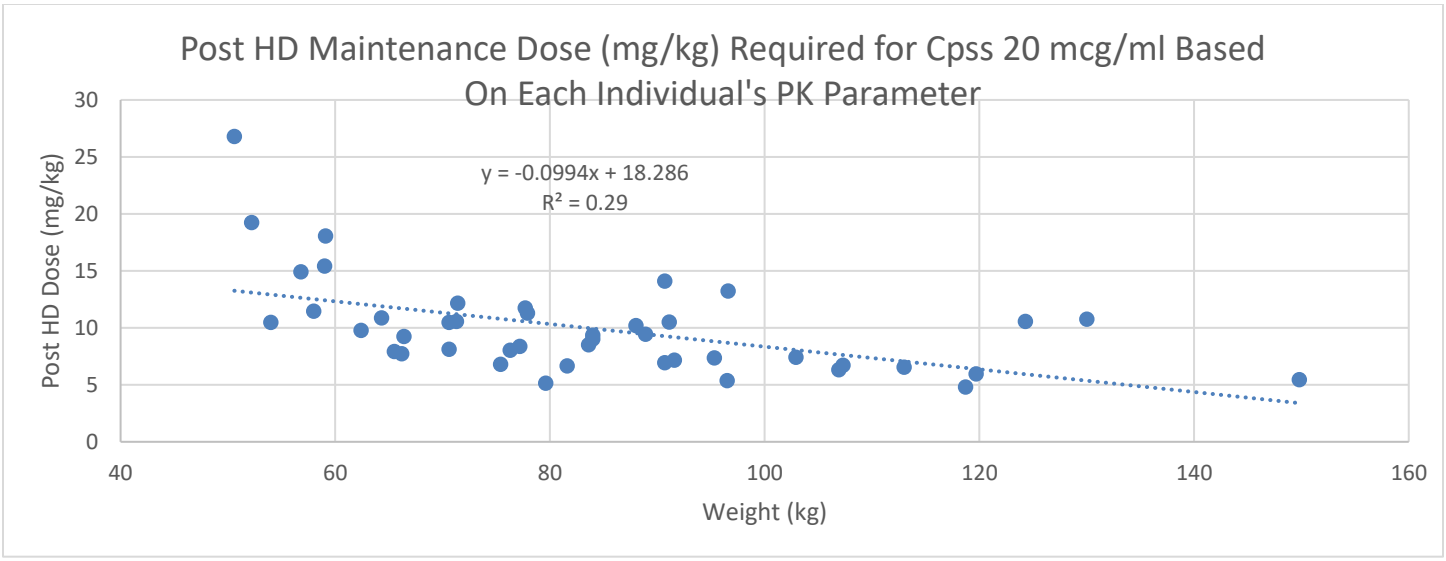
- Post hemodialysis doses should be given as soon as possible post dialysis to minimize the length of time of potentially subtherapeutic levels. A standard time of post hemodialysis dosing is not recommended.

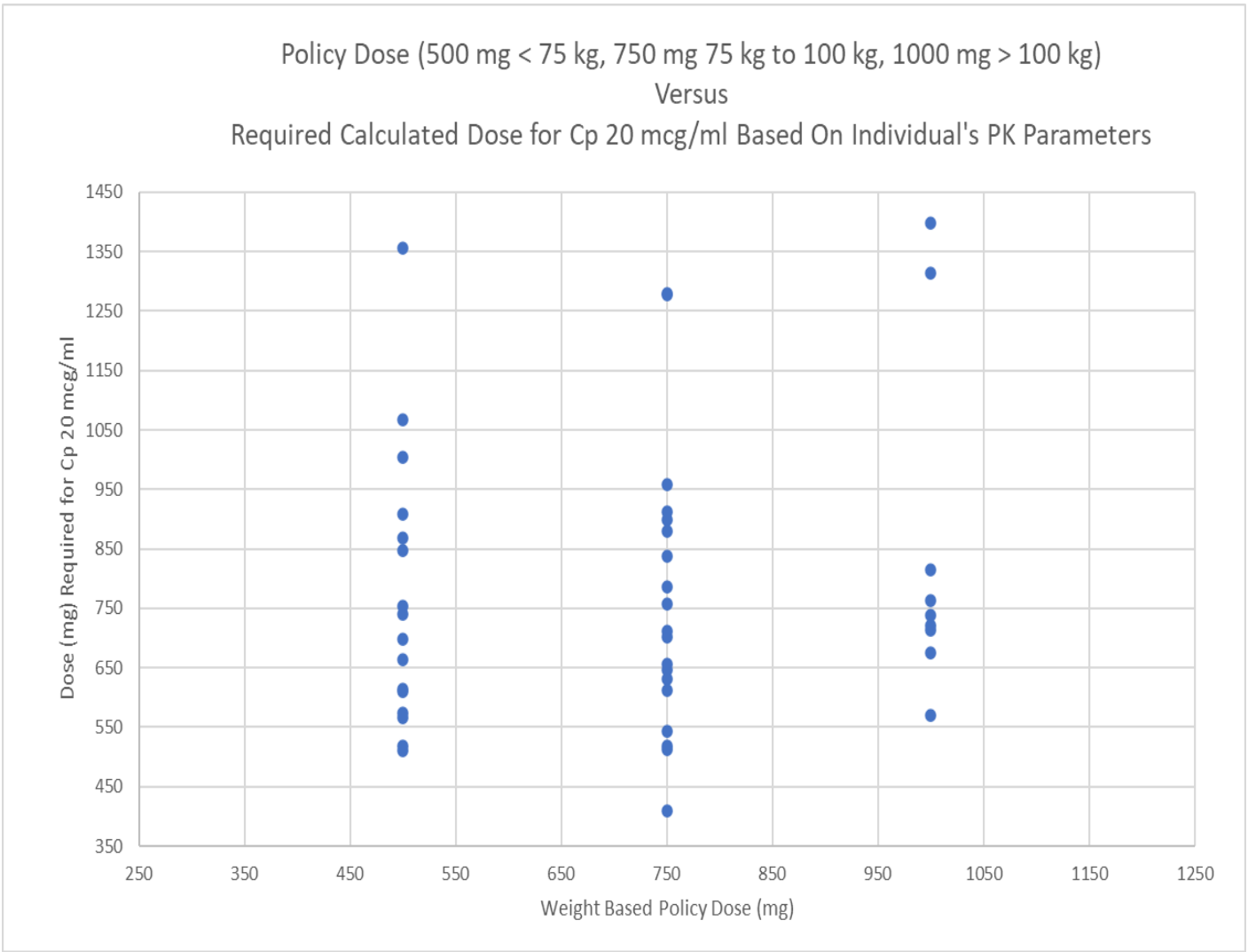


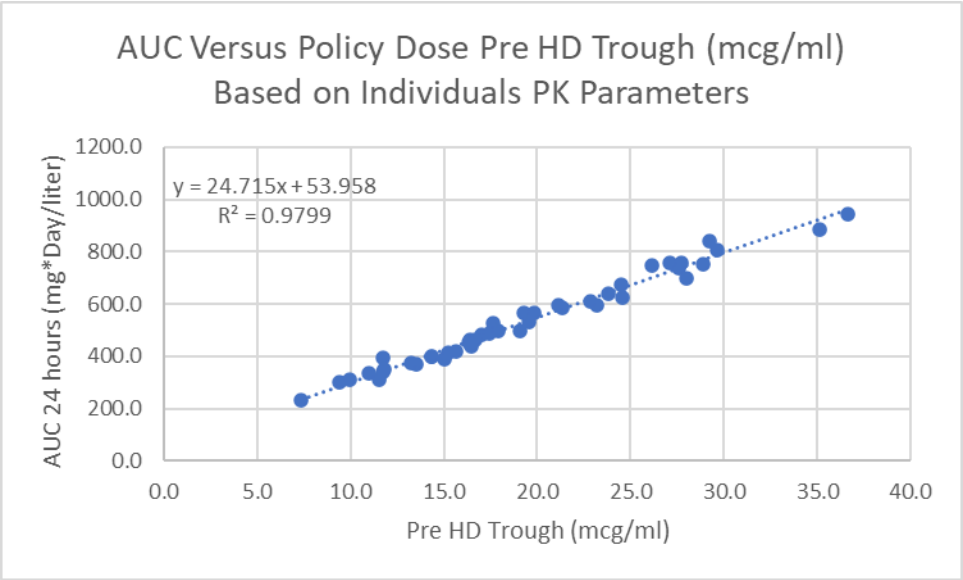



Each Individual's Weight Versus Average of Each Individual's Maintenance Dose
y = 3.5996x + 454.42
R² = 0.2335
Average of Individual's Maintenance Dose (mg)
Weight (kg)
0
200
400
600
800
1000
1200
0
20
40
60
80
100
120
140
160


Post HD Maintenace Dose (mg) Require for Cpss 20 mcg/ml Based On Each Individual's PK Parameter
y = 1.7907x + 634.52
R² = 0.0278
Post HD Dose (mg)
Weight (kg)
0
200
400
600
800
1000
1200
1400
1600
40
60
80
100
120
140
160


Post HD Maintenance Dose (mg/kg) Required for Cpss 20 mcg/ml Based On Each Individual's PK Parameter
y = -0.0994x + 18.286
R² = 0.29
Post HD Dose (mg/kg)
Weight (kg)
0
5
10
15
20
25
30
40
60
80
100
120
140
160


Policy Dose (500 mg < 75 kg, 750 mg 75 kg to 100 kg, 1000 mg > 100 kg)
Versus
Required Calculated Dose for Cp 20 mcg/ml Based On Individual's PK Parameters
Dose (mg) Required for Cp 20 mcg/ml
Weight Based Policy Dose (mg)
350
450
550
650
750
850
950
1050
1150
1250
1350
1450
250
350
450
550
650
750
850
950
1050
1150
1250


AUC Versus Policy Dose Pre HD Trough (mcg/ml)
Based on Individuals PK Parameters
y = 24.715x + 53.958
R² = 0.9799
AUC 24 hours (mg*Day/liter)
1200.0
1000.0
800.0
600.0
400.0
200.0
0.0
0.0
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
Pre HD Trough (mcg/ml)