SHC Vancomycin Dosing Guide

A. Initial Dosing Considerations

1. Review the following prior to initiation of therapy:
    a. Indication, relevant and pending microbial culture(s)
    b. Age, gender, height, weight, BMI
    c. Renal replacement therapy
    d. Special populations (obese, elderly, severely malnourished [BMI<16], amputees, pregnancy)
    e. Prior vancomycin dosing history (if applicable)
    f. Potential drug interactions
    g. Serum creatinine (SCr), urine output (if available), creatinine clearance (CrCl)
        i. Calculate CrCl using the Cockcroft-Gault equation (Figure 1)
            a) Elderly or severely malnourished: rounding SCr up is associated with underestimation of CrCl- clinical discretion advised [Smythe 1994, Young 2017, Barber 2016, Winter 2012]
            b) Use ideal body weight (IBW) for non-obese patients
            c) Use adjusted body weight (ABW) for obese patients [total body weight (TBW) $\geq$20% of IBW or BMI $\geq$30 kg/m^2]
            d) Use total body weight (TBW) if TBW < IBW

Figure 1. Cockroft-Gault Equation

$$\frac{CrCl\ \left(\frac{ml}{min}\right) = (140 - age)\ x\ IBW\ (x\ 0.85\ for\ females)}{SCr\ x\ 72}$$

IBW (male) = 50 kg + (2.3 x height in inches > 60 inches)
IBW (female) = 45 kg + (2.3 x height inches > 60 inches)
ABW (kg) = IBW + 0.4 (TBW – IBW)

h. Adverse Effects
    i. Red Man Syndrome is characterized by hypotension and/or a maculopapular rash appearing on the face, neck, trunk, and/or upper extremities.
    ii. If this occurs, pharmacist may slow the infusion rate (e.g. to 90-120 mins per 1 gm.) ± increase the dilution volume upon provider request ± recommend diphenhydramine 25-50mg premedication to the provider

B. Pharmacodynamic Targets: goal AUC and troughs

Indication	Target PD Index
Most indications	
AUC-based protocol	AUC 400-700
Trough-based protocol (dialysis, dose-by-level)	Trough ~15 (10-20)
Meningitis (empiric or definitive) **MRSA infections with vanco MIC = 2**	
AUC-based protocol	AUC 600-800
Trough-based protocol (dialysis, dose-by-level)	Trough 15-20
• **In general, goal AUC/MIC ≥ 400 for *S.aureus*** • **Monitor closely with trough > 15 or AUC > 700: increased risk of nephrotoxicity** • **Vancomycin may be continued in clinically responding patients with MRSA w/vancomycin MIC = 2**	

Exclusions from AUC-based dosing: rapidly fluctuating SCr, AKI (see section D footnote), renal replacement therapy

C: Loading dose

I. **Purpose**:

Ensures (Area Under Curve)/(Minimum Inhibitor Concentration) of >400 mcg-h/mL is achieved on day 1 of therapy for bacterial killing in in vitro and clinical outcomes in vivo studies

II. **Targeted populations**:

- Preferred in <u>seriously ill</u> (e.g. severe sepsis or septic shock requiring coverage for *S. aureus*)

III. **Standard load for patients with normal renal function: 25-30mg/kg TBW**

Patient Weight	Standard Loading Dose ~25 mg/kg TBW	Modified Loading Dose 15-20 mg/kg TBW Obese (BMI ≥ 30) CrCL < 30 or AKI, IHD, CRRT, unavailable Scr in emergent situations (e.g code sepsis or ED)
36 – 45 kg	1,000 mg x 1	750 mg x 1
46 – 55 kg	1,250 mg x 1	1,000 mg x 1
56 – 65 kg	1,500 mg x 1	1,250 mg x 1
66 – 75 kg	1,750 mg x1	1,500 mg x 1
76 – 120 kg	2,000 mg x 1	1,750 mg x1
> 120 kg	2,000 mg x 1	2,000 mg x 1

*Time maintenance dose start based on renal function: e.g. wait 24h to start maintenance regimen if CrCl = 30
Use total body weight (TBW); Round doses to nearest 250mg. Infuse each 1000mg over 60 minutes.

D: Initial Vancomycin Maintenance Dosing and Initial/Repeat Monitoring

I. **Round** doses to nearest 250mg
II. **Maximum dose**: 2gm per dose and 4.5g per 24h initially (including load)
III. **Repeat Vancomycin Levels**
  - **A.** After the target AUC or trough level is achieved at steady state, trough levels should be checked every 2 to 5 days until completion of therapy or discharge. Check peak/trough after any dose initiation/change.
    i. Levels should be checked sooner when clinically warranted (i.e.: change in clinical status or renal function, concern of accumulation/supratherapeutic levels, ≥25% change in trough/SCr)
  - **B.** If follow-up trough is within expected range, the AUC is likely within range as well
  - **C.** If follow-up trough is outside expected range, obtain another level to recalculate AUC
  - **D.** Troubleshooting: if a level is missed, draw level with the next dose if at steady state. Otherwise, re-send new paired peak/trough

IV. **Repeat SCr**: q1-3 days if hemodynamically stable. Check daily if at high risk of nephrotoxicity.
V. **Can calculate an estimated total daily dose using PK equations (see Part G) or use the table below**

Creatinine Clearance (mL/min)	Dose & Frequency Total body weight (TBW)	TDD Range	Timing of Peak/Trough Levels
> 90	15 mg/kg Q8-12H BMI ≥ 30: 10 – 15 mg/kg TBW Q12H† BMI ≥ 40: 7.5 – 12.5 mg/kg TBW Q12H†	30 – 45 mg/kg/day Obese: 15 – 30 mg/kg_{TBW}/day	Peak 1hr after 4th / trough 30 min before 5th dose, or Peak 1hr after 3rd/ trough 30 min before 4th dose
51-89	10– 20 mg/kg Q12H BMI ≥ 30: 10 – 12.5 mg/kg TBW Q12H† BMI ≥ 40: 7.5 – 10 mg/kg TBW Q12H†	20– 40 mg/kg/day Obese: 15 – 25 mg/kg_{TBW}/day	Q12H: Peak 1hr after 4th / trough 30 min before 5th dose, or Peak 1hr after 3rd/ trough 30 min before 4th dose
30-50	10-15 mg/kg Q12H to 20 mg/kg Q24H	20 – 30 mg/kg/day	Q12H: as above Q24H: Peak 1hr after 3rd/ trough 30 min before 4th dose
10-29	10 – 15 mg/kg Q24H to 15 mg/kg Q48H	7.5 – 15 mg/kg/day	Q24H – Peak 1hr after 3rd/ trough 30 min before 4th dose Q48H – Peak 1hr after 2nd dose; trough 30 min before 3rd dose
<10 or AKI*, dose by level	15 mg/kg x1, then dose by level	N/A	Trough within 24 hours of last dose, or with AM labs or every other day
Hemodialysis	Initial: 15 – 20 mg/kg x 1 (max 2gm) Maintenance: see appendix E	N/A	• Single pre-dialysis level (preferred) • Alternative: single level 4 hours after completion of dialysis session
CRRT‡	Initial: 15 – 20 mg/kg x 1 (max 2gm) Maintenance: 10 – 15 mg/kg Q24H	N/A	Trough 30 min before 3rd or 4th dose
Peritoneal dialysis	10 – 15 mg/kg IV x1, then dose by level	N/A	Check level 24h after initial dose. Consult ASP
	Dosing for intraperitoneal (IP) instillation (*NOT part of protocol*) [Li, 2016] Intermittent (1 exchange/day): 15-30mg/kg IP initially, then dose by level* *supplemental doses may be needed for APD patients		Intraperitoneal dosing (*off-protocol*): Level with AM labs on day 3 after any dose administered (allow fluid redistribution before drawing random level)

† Note: For those with $CrCL_{adjBW}$ > 120mL/min, Q8H may be considered if t½ < 8hr**
‡ *Loading and maintenance doses are based on 1-2L/hr dialysate flow and ultrafiltration rates, which is estimated to mimic a creatinine clearance of 30-50 mL/min*
***AKI (based on KDIGO, RIFLE, AKIN classifications):**
i. **SCr change by ≥ 0.3 mg/dL within 48h or 50% from baseline or within last 7 days**
ii. **CrCl change by >25 - 50%**
iii. **Urine output < 0.5 mL/kg/hr over 6 hours (oliguria)**

****Calculating t½ in obesity**

Step	Equation (adjusted for obese)
1	CL vanco = $CrCl_{adjBW}$ x 0.06 (see right table)
2	V_d = (0.5 – 0.7, see right table) x TBW
3	k = CL_{vanco}/V_d
4	t½ = 0.693/k

Modified CLvanco	
BMI ≥ 40 kg/m²	max CL ~7
Modified Vd	
BMI 30-40 kg/m²	~0.7 L/kg
BMI ≥ 40 kg/m²	0.5 – 0.6 L/kg

E: Dose Revisions

AUC calculator: This calculator is based on the Sawchuk-Zaske method and the equations used are summarized here.[11] Click here for link to AUC calculator on Microsoft Excel.

$$AUC = \frac{t\ (Cmax + Cmin)}{2} + \frac{Cmax - Cmin}{k}$$

t = infusion duration, $k = \frac{ln\frac{C_1}{C_2}}{\Delta t}$

- This AUC value applies to that calculated in a single dosing interval Δt → must be multiplied by the dosing frequency when applicable to obtain the total $AUC_{0\text{-}24}$
- *Cmax* (true peak) and *Cmin* (true trough) are back-calculated from measured values using this equation: $\boldsymbol{C_2 = C_1 \times e^{-k\,t}}$. (Details are in Part G)

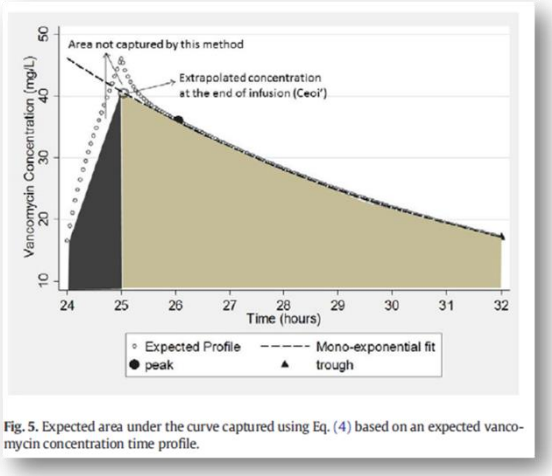


Fig. 5. Expected area under the curve captured using Eq. (4) based on an expected vancomycin concentration time profile.

Linear proportion method: Once a calculated AUC or trough is obtained, changes to the total daily dose (TDD) have a corresponding proportional change in troughs and AUCs when maintaining the same dosing interval, **assuming stable renal function and steady state conditions.**

$$\frac{AUC\ (calculated)}{AUC\ (desired)} = \frac{Current\ TDD}{New\ TDD} \qquad \frac{Cmin\ (observed)}{Cmin\ (desired)} = \frac{Current\ TDD}{New\ TDD}$$

E.g.: 1250mg IV Q12H results in an AUC of 800. To target a AUC 600, reduce to 1g q12h (rounded up from 1875mg/day). Alternatively, converting the same TDD to a q8h regimen would result in a higher trough but would not impact the AUC.

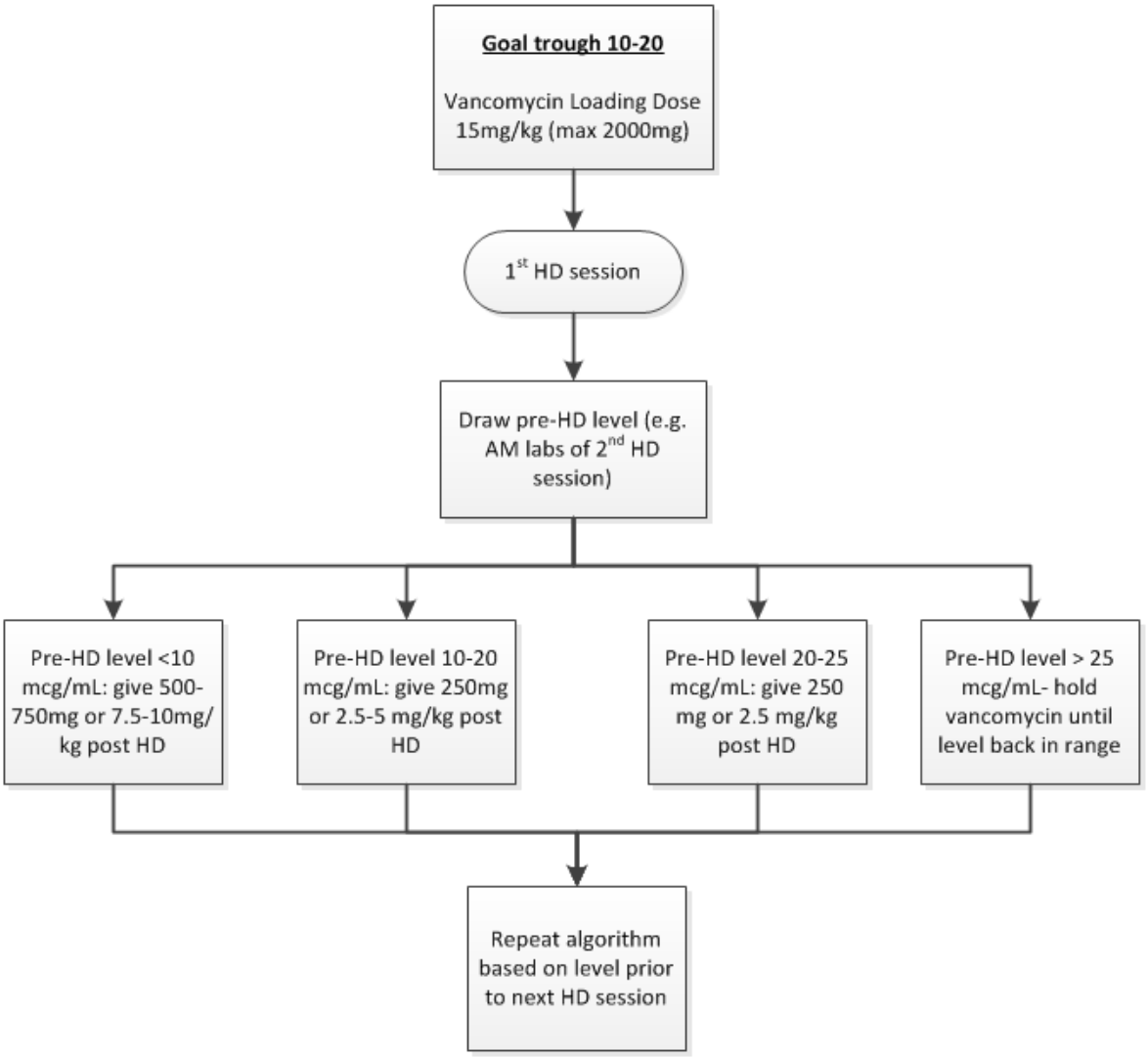
$$New\ TDD = \frac{600\ x\ 2500mg}{800} = 1875mg$$

Supratherapeutic levels and/or AKI: general approach

A. Do not restart vancomycin until the random/trough level is estimated or confirmed to be at/near 10-20 mg/dl. Allow sufficient time for drug clearance before restarting next dose.
B. Actions may include: pre-emptive dose adjustment, holding dose, checking level, discussion with provider, reassessing the need for vancomycin therapy.
C. Consider SCr/renal trajectory when determining next dose and/or level
    1. Ex) rapidly declining Scr may indicate improving renal function warranting earlier redosing vs. rapidly rising Scr indicating ongoing AKI- dose by level may be indicated

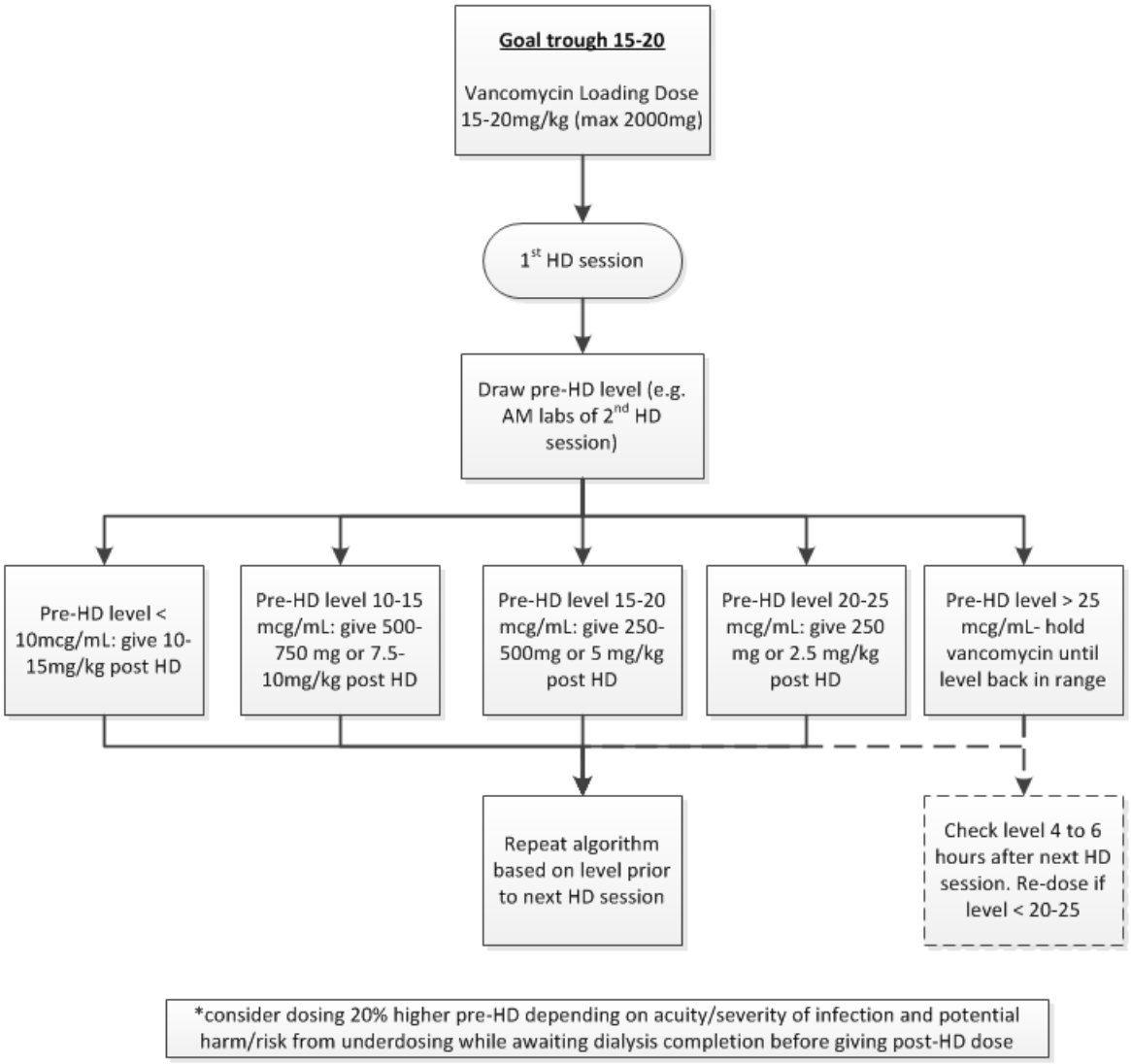
F: Intermittent Hemodialysis Dosing Algorithms

For goal trough 10-20 mcg/ml (~15):



*consider dosing 20% higher pre-HD depending on acuity/severity of infection and potential harm/risk from underdosing while awaiting dialysis completion before giving post-HD dose

For goal trough 15-20 mcg/ml:



G: PK Equations (same as those used in SHC Vancomycin Excel AUC Calculator)

AUC-based dosing: initial dosing

1. Step 1: estimate Cl_{vanco} (L/hr)= k_e x V_d
   a. In general populations: Matzke Equation: k_e = 0.00083 x CrCl +0.0044
   b. In obese patients: Crass et al 2018: Cl_{vanco}= 9.656-0.078 x age – 2.009 x SCr + 1.09 x sex + 0.04 x $TBW^{0.75}$, where female = 0 and male = 1.
      i. Reference: doi:10.1093/jac/dky310
2. Step 2: estimate total daily dose = Cl_{vanco} x goal $AUC_{0\text{-}24}$

AUC-based dosing: revision from 2 levels

Step	Description	Equation
1	Verify that doses were given on time and drawn appropriately	
2	Calculate the patient's observed k_e from 2 levels	$k_e = \frac{ln\frac{C_1}{C_2}}{t_2 - t_1}$ where C_1 usually is the peak, C_2 is usually the trough
3	Calculate half-life, $t_{1/2}$	$t_{1/2} = \frac{0.693}{k}$
4	Calculate true peak, C_{max}	$C_{max} = \frac{C_1}{e^{-k\,\Delta t}}$, Δt = time between end of infusion and time level drawn
5	Calculate true trough, C_{min}	$C_{min} = C_{max} \times e^{-ke \times (tau - t)}$ where t = infusion time
6	Calculate V_d (steady state conditions) *optional step: not required to determine AUC*	$V_d = \frac{Dose \times (1 - e^{-k \cdot t})}{t \times k_e \,(C_{max} - [C_{min} \times e^{-k \cdot t}])}$ where t = infusion time
7	Calculate vancomycin clearance *optional step: not required to determine AUC*	$CL_{van} = V_d \times k_e$
8	If C_{min} is high, calculate the time needed to reach desired range	*Time for C_{min} to reach $C_{desired}$* = $\frac{ln\frac{C_{min}}{C_{desired}}}{k_e}$
9	Calculate AUC during infusion using linear trapezoidal rule	$AUC_{inf} = t \times \frac{(C_{max} + C_{\min})}{2}$
10	Calculate AUC during elimination using logarithmic trapezoidal rule	$AUC_{elim} = \frac{(C_{max} - C_{\min})}{k_e}$
11	Calculate AUC_{24}	$AUC_{0-24} = (AUC_{inf} + AUC_{\text{elim}}) \times \frac{24}{tau}$
12	Estimate total daily dose need to achieve target AUC_{24} *Tip: new tau = 1 to 1.5x the half-life*	$New\ TDD = Current\ TDD \times \frac{AUC_{0-24}\ (desired)}{AUC_{0-24}\ (calculated)}$
13	Calculate predicted steady state C_{max} for new dosing regimen	$C_{ss,max} = \frac{New\ dose}{CL \times t} \times \frac{1 - e^{-k \cdot t}}{1 - e^{-k \cdot tau}}$
14	Calculate predicted steady state C_{min} for new dosing regimen	Same as step 5
15	Calculate predicted AUC based on new dosing regimen	Same as steps 9-11

Adapted from Detroit Medical Center: "Vancomycin Dosing in Adults- Clinical Guidelines" Jan 2015 and https://pharmacy.ufl.edu/files/2013/01/5127-28-equations.pdf, accessed June 6, 2018.

Abbreviations

t: infusion time; tau: dosing interval; Ke: elimination rate constant; Vd: volume of distribution; C_1: concentration at time t_1 (i.e. first of 2 levels drawn following dose); C_2: concentration at time t_2 (i.e. second of 2 levels drawn following dose) t_1: time at which C_1 is drawn t_2: time at which C_2 is drawn CL_{van}: vancomycin clearance TDD: total daily dose AUC: area under the concentration-time curve AUC_{24}: 24 hour area under the concentration-time curve