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 [BMI ≥30 kg/m^2]

    Use total body weight (TBW) if TBW < IBW

Figure 1. Cockgroft-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. "Vancomycin infusion reaction" 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 – 600 mg*h/L
Trough-based protocol (IHD, PD, nocturnal CRRT, dose-by-level)	Trough ~15 (10-20) mg/L
Continuous IV infusion	Random 17-25 mg/L
Meningitis/ventriculitis (empiric or definitive)	
Trough-based protocol	Trough 15-20 mg/L
• **In general, goal AUC/MIC ≥ 400 for *S.aureus***	
• **Monitor closely with trough > 15 or AUC > 650: increased risk of nephrotoxicity**	
• **Vancomycin may be continued in clinically responding patients with MRSA w/vancomycin MIC = 2; consider ASP or ID consult**	

†Exclusions from AUC-based dosing: rapidly fluctuating SCr, AKI (see section D footnote), intermittent hemodialysis (IHD), peritoneal dialysis (PD), nocturnal CRRT, CNS infections

C: Loading dose

I. **Purpose**:

Achieves rapid attainment of targeted concentrations and AUC/MIC of >400 mg-h/L on day 1 of therapy for bacterial killing in in vitro and clinical outcomes in vivo studies

II. **Targeted populations**:

- Preferred in seriously and/or critically-ill patients with suspected or documented serious MRSA infections (e.g. severe sepsis or septic shock requiring coverage for *S. aureus*)

III. **Standard load for patients with normal renal function: 20-35mg/kg TBW (maximum 3g)**

The decision of whether to employ a loading dose, as well as the magnitude of this dose, should be driven by the severity of infection and the urgency to achieve a therapeutic concentration rather than body size alone. InsightRX has a loading dose feature that can help simulate exposure.

Patient Weight	Standard Loading Dose ~25 mg/kg TBW	Modified Loading Dose 20-25 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	2,000-3,000 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**: 2g per dose and 4.5g per 24 hours initially (including load)
III. **Vancomycin Levels with InsightRX**
  - **A.** Initial: A single level should be drawn within the first 24-48 hours after the first dose.
    - i. An earlier initial level may be helpful in ensuring therapeutic concentrations in certain clinical scenarios (i.e. critically ill patients, patients with high or low BMI, etc.)
    - ii. Levels may be drawn at any point during the dosing interval (except during infusion or distribution phase) and do not need to be drawn at steady state with InsightRX
    - iii. Consider drawing two levels to improve predictions in certain patients, such as those with obesity, critical illness, low SCr due to low muscle mass, or intermediate/poor model fit
      1. These levels do not have to be from the same dosing interval, but should ideally be drawn at different time points of the dosing interval (i.e. not two troughs)
  - **B.** Repeat: If dosing parameters remain stable (i.e. renal function, weight, etc.) and the model fit seems appropriate, repeat levels may be spaced out (i.e. after 48-72 hours). Changes in dosing parameters or dose should prompt repeat levels.
IV. **Repeat SCr**: q1-3 days if hemodynamically stable. Check daily if at high risk of nephrotoxicity.
V. **Estimate dose based on renal function/renal replacement modality**

Creatinine Clearance (mL/min)	Dose & Frequency Total body weight (TBW)	Timing of Levels
>130	ICU only: 15mg/kg x1 (max 3g), then use InsightRX for continuous infusion dose	Random level 24 hours after start of infusion
10-129	Use InsightRX (refer to Appendix A: section A for general dosing guidance if model does not fit well and predicted regimens seem clinically inappropriate)	Initial level drawn within first 24-48 hours after initial dose (drawn at least 1hr after end of infusion)
<10 or AKI*, dose by level	15 mg/kg x1, then dose by level	Trough within 24 hours of last dose, or with AM labs or every other day
Hemodialysis	Initial: ~ 20-25 mg/kg x 1 (max 2gm) Maintenance: see section F	Single pre-dialysis level (preferred) Alternative: single level 4 hours after completion of dialysis session
CRRT‡ or nocturnal CRRT	Initial: 20-25 mg/kg x 1 (max 2gm) Maintenance: 10 – 15 mg/kg Q24H	Q24H: Peak 1hr after 2nd or 3rd dose; Trough 30 min before 3rd or 4th dose, respectively
Peritoneal dialysis	10 – 15 mg/kg IV x1, then dose by level	Check level 24h after initial dose. Consult ASP
	Dosing for intraperitoneal (IP) instillation: see Lexicomp (*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)

‡ *Loading and maintenance doses based on 1-2L/hr dialysate flow and ultrafiltration rates, approximates CrCL 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)
iv. SCr ≥0.5 mg/dL, or a 50% increase from baseline in consecutive daily readings, or a decrease in CrCl of 50% from baseline on 2 consecutive days in the absence of an alternative explanation

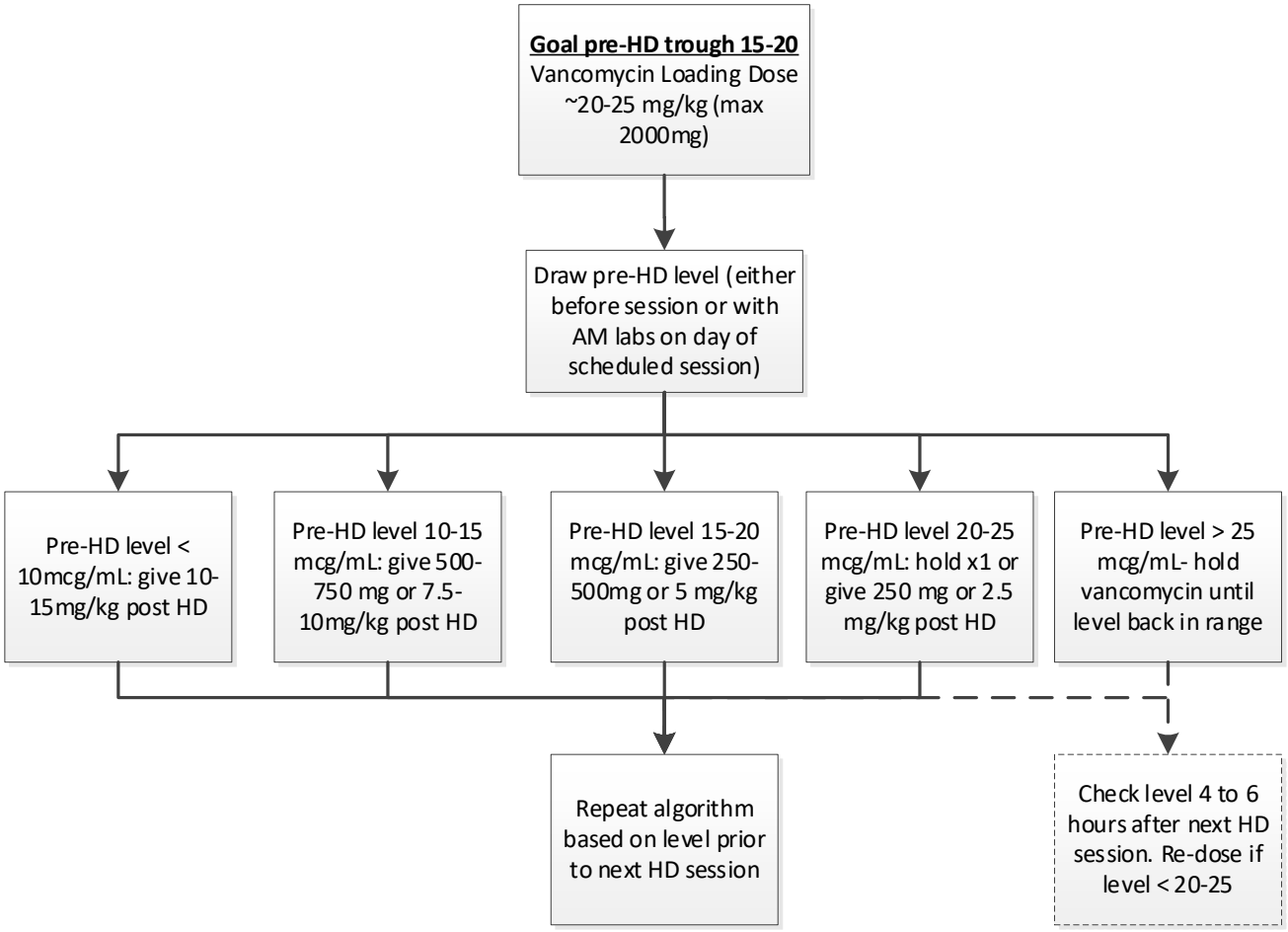
E: Dose Revisions

InsightRX uses Bayesian software to predict vancomycin exposure based on pharmacokinetic modeling and patient-specific information (i.e. creatinine, prior vancomycin levels). See SHC InsightRX Vancomycin Tip Sheet for more information.

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. Predictive graphs on InsightRX may aid in predicting when levels will decline below supratherapeutic.
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 Algorithm



*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

G: Continuous Infusion Vancomycin

Indicated Populations:

- Critically ill patients with augmented renal function defined as CrCl > 130 ml/min

Exclusions:

- Anticipated therapy <48 hours (ex: treatment of empiric pulmonary infection where nasal PCR and provide quick de-escalation, post-op prophylaxis)
- History of neuro-muscular disease, quadriplegia/paraplegia (disease states resulting in low SCr and falsely elevated CrCl)
- Age > 50 years
- Weight < 50 kg
- Meningitis

Administration

- **Infusion Time (Loading Dose):** Total dose to be given as 1000 mg/hour
- **Infusion Time (Maintenance Dose):** Total dose to be given over 24 hours starting immediately after initial dose.

Initial Dosing: use total body weight (TBW) for dosing

	Loading Dose	Maintenance
Augmented Renal Function	15 mg/kg TBW [max 3000 mg]	Calculate 24-hour requirement using: InsightRX (custom dose with infusion length over 24 hours)

Monitoring

- Draw a random level at 24 hours after the start of the continuous infusion
- Goal level: 17-25 mg/L
    - If therapeutic: recheck another level at 72 hours; earlier if changes in renal function suspected to lead to out of range level, e.g. SCr change > 25%
    - If subtherapeutic: increase the dose (see adjusting doses below) and recheck level in 24 hours
    - If supratherapeutic: hold dose and reduce the dose (see adjusting doses below) and recheck level in 24 hours

Converting Between Intermittent Dosing and Continuous Dosing:

- Patients who are therapeutic on intermittent dosing do not require a loading dose
- Patients on continuous infusion vancomycin therapy may accumulate vancomycin and therefore may require lower total daily doses compared to intermittent therapy
    - If patients therapeutic on intermittent dosing
        - Add up total daily vancomycin dose
        - Reduce by 10-15%
        - Round to the nearest 250 mg (this will be the starting dose of continuous infusion)
    - If patients are sub-therapeutic or supra-therapeutic on intermittent dosing
        - Dosing for continuous infusion should be calculated on a case-by-case basis using existing data.
    - Can use InsightRX to guide dosing

H: Discharge on vancomycin

General approach for discharge: specify desired vancomycin trough range based on prior trough levels associated with therapeutic AUC

- Select a trough range as approximately +/- 2 of the trough level corresponding to target AUC, assuming the AUC is not already at the upper or lower limits. Please use clinical discretion.

Goal vancomycin troughs for discharge

Description	Target trough range	Notes
Prior therapeutic AUC available	Individualized: select a 5-point range close to trough associated with therapeutic AUC (400-600 mg*h/L)	• Ex 1. if trough was 12 with AUC 500, discharge target trough range 10-15 mg/L. • Ex 2. if trough was 12 with AUC 400, discharge target trough range 12-17 mg/L. <u>Option to calculate:</u> Calculate lower (x) and upper (y) limits of target range using linear proportionality • Using Ex 1 above: o Lower limit: 12/500=x/400 = 9.6 ≈ 10 o Upper limit: 12/500 = y/600=14.4 ≈ 15
No prior therapeutic AUC available	12-17 mg/L	
Intermittent hemodialysis	15-20 mg/L	
Continuous infusion	Random level: 17-25 mg/L	• Logistical barriers: requires advanced planning with case management for insurance approval, ensure outpatient pharmacy or SNF feasibility, etc. o Related info: see Section G for how to transition off continuous infusion

I. DOCUMENT INFORMATION

A. Original Author/Date
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B. Gatekeeper
Pharmacy Department

C. Distribution
This procedure is kept in the Pharmacy Policies and Procedure Manual

D. Review/Revision History:
Lina Meng, PharmD: 06/2015
Janjri Desai, PharmD: 10/2015, 03/2016, 08/2016
Lina Meng, PharmD: 08/2016, Emily Mui, PharmD: 08/2016
Calvin Diep, PharmD; Liz Keil, PharmD; Jamie Kuo, PharmD; Lina Meng, PharmD: 05/2021, 01/2022
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E. Approvals
Antibiotic Subcommittee: 08/2013, 11/2016, 10/2020, 05/2021, 03/2022, 03/2023
Pharmacy and Therapeutics Committee: 11/2015, 03/2016, 05/2021, 04/2022

APPENDIX A: Vancomycin dosing via PK equations/AUC calculator

A: Initial Vancomycin Maintenance Dosing and Initial/Repeat Monitoring (AUC calculator)

I. **Round** doses to nearest 250mg
II. **Maximum dose**: 2gm per dose and 4.5g per 24 hr 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 <u>within</u> expected range, the AUC is likely within range as well
- **C.** If follow-up trough is <u>outside</u> 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

Expected target trough range correlating to AUC	**Examples**
Individualized: select a 5-point range close to trough associated with therapeutic AUC (400-600 mg*h/L) See Excel calculator	• Ex 1. if trough was 12 with AUC 500, target trough range 10-15 mg/L. • Ex 2. if trough was 12 with AUC 400, target trough range 12-17 mg/L. <u>Option to calculate:</u> Calculate lower (x) and upper (y) limits of target range using linear proportionality • Using Ex 1 above: o Lower limit: 12/500=x/400 = 9.6 ≈ 10 o Upper limit: 12/500 = y/600=14.4 ≈ 15

IV. **Repeat SCr**: q1-3 days if hemodynamically stable. Check daily if at high risk of nephrotoxicity.
V. **Preferred: estimate total daily dose using PK equations (see Part H) – see Excel calculator**

Creatinine Clearance (mL/min)	**Dose & Frequency** Total body weight (TBW)	**TDD Range**	**Timing of Peak/Trough Levels**
>130	ICU only: 15mg/kg x1 (max 3g), then use PK calculator for daily dose given as continuous infusion	40-45 mg/kg	Random level 24 hours after start of infusion
> 90	15 mg/kg Q8-12H† Obese: use PK calculator	30 – 45 mg/kg/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 Obese: use PK calculator	20– 40 mg/kg/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 Obese: use PK calculator	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 Obese: use PK calculator	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
CRRT‡ or nocturnal CRRT	<u>Initial</u>: 20-25 mg/kg x 1 (max 2gm) <u>Maintenance</u>: 10 – 15 mg/kg Q24H	N/A	Q24H: Peak 1hr after 2nd or 3rd dose; Trough 30 min before 3rd or 4th dose, respectively

† <u>Note</u>: For those with $CrCL_{adjBW}$ > 120mL/min, Q8H may be considered if t½ < 8hr (use Excel for t½ calculation, or appendix G)
‡ *Loading and maintenance doses based on 1-2L/hr dialysate flow and ultrafiltration rates, approximates CrCL 30-50 mL/min*

B: Dose Revisions (AUC calculator)

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: $\boldsymbol{C_2 = C_1 \times e^{-kt}}$. (Details are in Part H)

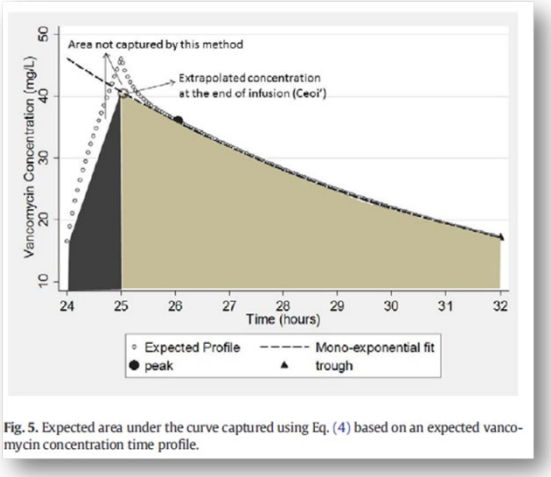

Fig. 5. Expected area under the curve captured using Eq. (4) based on an expected vancomycin concentration time profile.

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 an 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.

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

C: Continuous Infusion Vancomycin (AUC calculator)

Initial Dosing: use total body weight (TBW) for dosing

	Loading Dose	Maintenance
Augmented Renal Function	15 mg/kg TBW [max 3000 mg]	Calculate 24 hour requirement using: AUC dosing calculator (tab 1 on excel file) SHC Vancomycin Dosing Calculator

Monitoring

•Draw a random level at 24 hours after the start of the continuous infusion
•Goal level: 17-25 mg/L

- If therapeutic: recheck another level at 72 hours; earlier if changes in renal function suspected to lead to out-of-range level, e.g. SCr change > 25%
- If subtherapeutic: increase the dose (see adjusting doses below) and recheck level in 24 hours
- If supratherapeutic: hold dose and reduce the dose (see adjusting doses below) and recheck level in 24 hours

Adjusting Doses:

- **Subtherapeutic or Supratherapeutic: Proportional calculation (assuming SCr stable)**

$$\frac{\text{Current 24-hour dose}}{\text{Current vancomycin level}} = \frac{\text{X (revised dose)}}{\text{Desired vancomycin level}}$$

* If supratherapeutic, may consider re-checking level and resume continuous infusion when level is < 25 mg/mL

Converting from Intermittent Dosing to Continuous Dosing:

- Patients who are therapeutic on intermittent dosing do not require a loading dose
- Patients on continuous infusion vancomycin therapy may accumulate vancomycin and therefore may require lower total daily doses compared to intermittent therapy
  - If patients therapeutic on intermittent dosing
    - Add up total daily vancomycin dose
    - Reduce by 10-15%
    - Round to the nearest 250 mg (this will be the starting dose of continuous infusion)
  - If patients are sub-therapeutic or supra-therapeutic on intermittent dosing
    - Dosing for continuous infusion should be calculated on a case-by-case basis using existing data.
    - Can use InsightRX to guide dosing

Converting from Continuous Dosing to Intermittent Dosing:

If therapeutic on continuous infusion vancomycin dosing, add up 24-hour dose and divide by appropriate dosing interval

D: 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}	$C_{max} = \frac{C_1}{e^{-k\,t'}}$, t' = time between C1 and end of infusion
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