SHC Vancomycin Dosing Guide

A: Initial dosing considerations

B. Pharmacodynamic Targets: goal AUC and troughs

C. Loading dose

D: Initial Vancomycin Maintenance Dosing and Serum Concentration Monitoring

E: Dose Revisions

F: Intermittent Hemodialysis Dosing Algorithms

G: PK equations

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) >20% of IBW or BMI >30 kg/m²]
         d) Use total body weight (TBW) if TBW < IBW

Figure 1. Cockcroft-Gault Equation

\[
\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{IBW} \times 0.85 \text{ for females}}{\text{SCr} \times 72}
\]

   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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target PD Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most indications</td>
<td></td>
</tr>
<tr>
<td>AUC-based protocol</td>
<td>AUC 400-700</td>
</tr>
<tr>
<td>Trough-based protocol (dialysis, dose-by-level)</td>
<td>Trough ~15 (10-20)</td>
</tr>
<tr>
<td>Meningitis (empiric or definitive)</td>
<td></td>
</tr>
<tr>
<td>MRSA infections with vanco MIC = 2</td>
<td></td>
</tr>
<tr>
<td>AUC-based protocol</td>
<td>AUC 600-800</td>
</tr>
<tr>
<td>Trough-based protocol (dialysis, dose-by-level)</td>
<td>Trough 15-20</td>
</tr>
</tbody>
</table>

- 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 seriously ill (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

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Standard Loading Dose 25 mg/kg TBW</th>
<th>Modified Loading Dose 15-20 mg/kg TBW</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 – 45 kg</td>
<td>1,000 mg x 1</td>
<td>750 mg x 1</td>
</tr>
<tr>
<td>46 – 55 kg</td>
<td>1,250 mg x 1</td>
<td>1,000 mg x 1</td>
</tr>
<tr>
<td>56 – 65 kg</td>
<td>1,500 mg x 1</td>
<td>1,250 mg x 1</td>
</tr>
<tr>
<td>66 – 75 kg</td>
<td>1,750 mg x 1</td>
<td>1,500 mg x 1</td>
</tr>
<tr>
<td>76 – 120 kg</td>
<td>2,000 mg x 1</td>
<td>1,750 mg x 1</td>
</tr>
<tr>
<td>&gt; 120 kg</td>
<td>2,000 mg x 1</td>
<td>2,000 mg x 1</td>
</tr>
</tbody>
</table>

*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/m² 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

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose &amp; Frequency</th>
<th>TDD Range</th>
<th>Timing of Peak/Trough Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 90</td>
<td>15 mg/kg Q8-12H</td>
<td>30 – 45 mg/kg/day Obese: 15 – 30 mg/kgTBW/day</td>
<td>Peak 1hr after 4th/ trough 30 min before 5th dose, or Peak 1hr after 3rd/ trough 30 min before 4th dose</td>
</tr>
<tr>
<td>51-89</td>
<td>10– 20 mg/kg Q12H</td>
<td>20– 40 mg/kg/day Obese: 15 – 25 mg/kgTBW/day</td>
<td>Q12H: Peak 1hr after 4th/ trough 30 min before 5th dose, or Peak 1hr after 3rd/ trough 30 min before 4th dose</td>
</tr>
<tr>
<td>30-50</td>
<td>10–15 mg/kg Q12H to 20 mg/kg Q24H</td>
<td>20 – 30 mg/kg/day</td>
<td>Q24H: Peak 1hr after 3rd/ trough 30 min before 4th dose</td>
</tr>
<tr>
<td>10-29</td>
<td>10 – 15 mg/kg Q24H to 15 mg/kg Q48H</td>
<td>7.5 – 15 mg/kg/day</td>
<td>Q48H – Peak 1hr after 2nd/ trough 30 min before 4th dose; trough 30 min before 3rd dose</td>
</tr>
</tbody>
</table>
| <10 or AKI†, dose by level   | 15 mg/kg x1, then dose by level | N/A | • Single pre-dialysis level (preferred)  
• Alternative: single level 4 hours after completion of dialysis session |

Hemodialysis

Initial: 15 – 20 mg/kg x 1 (max 2gm)  
Maintenance: see appendix E  
N/A  
Trough 30 min before 4th dose

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

Dosing for intraperitoneal (IP) instillation (NOT part of protocol) [Li, 2016]  
Intermittent (1 exchange/day): 15-30mg/kg IP initially, then dose by level*  
N/A  
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_adj ≤ 100 mL/min, QBH may be considered if t½ < 8h
‡ 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

<table>
<thead>
<tr>
<th>Step</th>
<th>Equation (adjusted for obese)</th>
<th>Modified CLvanco</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CL vanco = CrClbaseline x 0.06 (see right table)</td>
<td>BMI ≥ 40 kg/m²</td>
</tr>
<tr>
<td>2</td>
<td>Vd = (0.5 – 0.7, see right table) x TBW</td>
<td>Modified Vd</td>
</tr>
<tr>
<td>3</td>
<td>k = CLvanco/Vd</td>
<td>BMI ≤ 30-40 kg/m²</td>
</tr>
<tr>
<td>4</td>
<td>t½ = 0.693/k</td>
<td>BMI ≥ 40 kg/m²</td>
</tr>
</tbody>
</table>
E: Dose Revisions

AUC calculator: This calculator is based on the Sawchuk-Zaske method and the equations used are summarized here.\(^\text{11}\) Click [here](#) for link to AUC calculator on Microsoft Excel.

\[
AUC = \frac{t (C_{\text{max}} + C_{\text{min}})}{2} + \frac{C_{\text{max}} - C_{\text{min}}}{k}
\]

\[t = \text{infusion duration}, \quad k = \frac{\ln C_1}{\Delta t}\]

- This AUC value applies to that calculated in a single dosing interval \(\Delta t\) → must be multiplied by the dosing frequency when applicable to obtain the total AUC\(_{0-24}\)
- \(C_{\text{max}}\) (true peak) and \(C_{\text{min}}\) (true trough) are back-calculated from measured values using this equation:
  \[C_2 = C_1 \times e^{-kt} \text{. (Details are in Part G)}\]

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.

\[
\frac{\text{AUC (calculated)}}{\text{AUC (desired)}} = \frac{\text{Current TDD}}{\text{New TDD}} \quad \frac{\text{C}_{\text{min}} \text{ (observed)}}{\text{C}_{\text{min}} \text{ (desired)}} = \frac{\text{Current TDD}}{\text{New TDD}}
\]

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.

\[
\text{New TDD} = \frac{600 \times 2500mg}{800} = 1875mg
\]

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):*

1. **Goal trough 10-20**
   - Vancomycin Loading Dose 15mg/kg (max 2000mg)

2. **1st HD session**

3. **Draw pre-HD level (e.g., AM labs of 2nd HD session)**

   - **Pre-HD level <10 mcg/mL:** give 500-750mg or 7.5-10mg/kg post HD
   - **Pre-HD level 10-20 mcg/mL:** give 250mg or 2.5-5 mg/kg post HD
   - **Pre-HD level 20-25 mcg/mL:** give 250 mg or 2.5 mg/kg post HD
   - **Pre-HD level > 25 mcg/mL:** hold vancomycin until level back in range

4. **Repeat algorithm based on level prior to next HD session**

*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:

Goal trough 15-20
Vancomycin Loading Dose
15-20 mg/kg (max 2000 mg)

1st HD session

Draw pre-HD level [e.g.
AM labs of 2nd HD
session]

Pre-HD level <
10 mcg/mL: give 10-
15 mg/kg post HD

Pre-HD level 10-15
mcg/mL: give 500-
750 mg or 7.5-
10 mg/kg post HD

Pre-HD level 15-20
mcg/mL: give 250-
500 mg or 5 mg/kg
post HD

Pre-HD level 20-25
mcg/mL: give 250
mg or 2.5 mg/kg
post HD

Pre-HD level > 25
mcg/mL: hold
vancomycin until
level back in range

Repeat algorithm
based on level prior
to next HD session

Check level 4 to 6
hours after next HD
session. Re-dose if
level < 20-25

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

**AUC-based dosing: initial dosing**

1. **Step 1: estimate** $CL_{vanco}$ ($L/hr$) = $k_e \times V_d$
   a. In general populations: Matzke Equation: $k_e = 0.00083 \times CrCl + 0.0044$
   b. In obese patients: Crass et al 2018: $CL_{vanco} = 9.656-0.078 \times age - 2.009 \times SCr + 1.09 \times sex + 0.04 \times TBW^{0.75}$, where female = 0 and male = 1.
2. **Step 2: estimate total daily dose** = $CL_{vanco} \times$ goal AUC$_{0-24}$

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


**Abbreviations**

$t$: infusion time; $tau$: dosing interval; $Ke$: elimination rate constant; $Vd$: volume of distribution; $C_t$: concentration at time $t$ (i.e. first of 2 levels drawn following dose); $C_p$: concentration at time $t_p$ (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; $CL_{vanco}$: vancomycin clearance; TDD: total daily dose; AUC: area under the concentration-time curve; $AUC_{24}$: 24 hour area under the concentration-time curve.