SHC Vancomycin Dosing Guide

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B. Pharmacodynamic Targets: goal AUC and troughs
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D: Initial Vancomycin Maintenance Dosing and Serum Concentration Monitoring
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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
   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

Figure 1. Cockcroft-Gault Equation

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

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)
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 - 600</td>
</tr>
<tr>
<td>Trough-based protocol</td>
<td>Trough ~15 (10-20)</td>
</tr>
<tr>
<td>Meningitis (empiric or definitive)</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 > 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), renal replacement therapy

C: Loading dose

I. Purpose:
Achieves rapid attainment of targeted concentrations and AUC/MIC of >400 mcg-h/mL 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: 25-35mg/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.

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Standard Loading Dose</th>
<th>Modified Loading Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>~25 mg/kg TBW</td>
<td>15-25 mg/kg TBW</td>
</tr>
<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 x1</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 x1</td>
</tr>
<tr>
<td>&gt; 120 kg</td>
<td>2,000-3,000 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: 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

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose &amp; Frequency Total body weight (TBW)</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 BMI ≥ 30: 10 – 15 mg/kg TBW Q12H† BMI ≥ 40: 7.5 – 12.5 mg/kg TBW Q12H†</td>
<td>30 – 45 mg/kg/day Obese: 15 – 30 mg/kg/adjBW/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 BMI ≥ 30: 10 – 12.5 mg/kg TBW Q12H† BMI ≥ 40: 7.5 – 10 mg/kg TBW Q12H†</td>
<td>20 – 40 mg/kg/day Obese: 15 – 25 mg/kg/adjBW/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>Q12H: as above 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 3rd/ trough 30 min before 4th dose Q48H – Peak 1hr after 2nd dose; trough 30 min before 3rd dose</td>
</tr>
<tr>
<td>&lt;10 or AKI*, dose by level</td>
<td>15 mg/kg x1, then dose by level</td>
<td>N/A</td>
<td>Trough within 24 hours of last dose, or with AM labs or every other day</td>
</tr>
</tbody>
</table>

Hemodialysis

Initial: 15 – 20 mg/kg x 1 (max 2gm) Maintenance: see appendix F

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

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

N/A

Intrapерitoneal 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 are based on 1-2L/hr dialysate flow and ultrafiltration rates, which is estimated to mimic a creatinine clearance of 30-50 mL/min

‡ Note: For those with CrCLadj > 120mL/min, Q8H may be considered if t½ < 8hr (use Excel for t½ calculation, or appendix G)

* 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)
E: Dose Revisions

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

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

- 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: $C_2 = C_1 \times e^{-kt}$. (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.

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

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 Algorithm

**Goal pre-HD trough 10-20**
(15-20 for MRSA)
Vancomycin Loading Dose
~20 mg/kg (max 2000mg)

Draw pre-HD level (either before session or with AM labs on day of scheduled session)

- Pre-HD level < 10mcg/mL: give 10-15mg/kg post HD
- Pre-HD level 10-15 mcg/mL: give 500-750 mg or 7.5-10mg/kg post HD
- Pre-HD level 15-20 mcg/mL: give 250-500mg or 5 mg/kg post HD
- Pre-HD level 20-25 mcg/mL: hold x1 or 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 $\text{Cl}_{\text{vanco}}$ (L/hr) = $k_e \times V_d$
   a. In general populations: Matzke Equation: $k_e = 0.00083 \times \text{CrCl} + 0.0044$
   b. In obese patients: Crass et al 2018: $\text{Cl}_{\text{vanco}} = 9.656 - 0.078 \times \text{age} - 2.009 \times \text{SCR} + 1.09 \times \text{sex} + 0.04 \times \text{TBW}^{0.75}$, where female = 0 and male = 1.

2. Step 2: estimate total daily dose = $\text{Cl}_{\text{vanco}} \times \text{goal AUC}_{0-24}$

**AUC-based dosing: revision from 2 levels**

<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>$k_e = \frac{\ln(C_2)}{t_{2-1}}$, 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>$C_{\text{max}} = \frac{C_1}{e^{-k \cdot \Delta t}}$, $\Delta t =$ time between end of infusion and time level drawn</td>
</tr>
<tr>
<td>5</td>
<td>Calculate true trough, $C_{\text{min}}$</td>
<td>$C_{\text{min}} = C_{\text{max}} \times e^{-k \times \tau}$ where $\tau =$ infusion time</td>
</tr>
<tr>
<td>6</td>
<td>Calculate $V_d$ (steady state conditions)</td>
<td>$V_d = \frac{\text{dose} \times (1-e^{-k \cdot \tau})}{k \times k_e (C_{\text{max}} - C_{\text{min}} e^{-k \cdot \tau})}$ where $\tau =$ infusion time</td>
</tr>
<tr>
<td>7</td>
<td>Calculate vancomycin clearance</td>
<td>$\text{CL}_{\text{van}} = V_d \times k_e$</td>
</tr>
<tr>
<td>8</td>
<td>If $C_{\text{min}}$ is high, calculate the time needed to reach desired range</td>
<td>$\text{Time for } C_{\text{min}} \text{ to reach } C_{\text{desired}} = \frac{\ln(C_{\text{desired}})}{k_e}$</td>
</tr>
<tr>
<td>9</td>
<td>Calculate AUC during infusion using linear trapezoidal rule</td>
<td>$AUC_{\text{inf}} = t \times \frac{(C_{\text{max}} + C_{\text{min}})}{2}$</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>$AUC_{0-24} = (AUC_{\text{inf}} + AUC_{\text{elim}}) \times \frac{24}{\tau_{\text{au}}}$</td>
</tr>
<tr>
<td>12</td>
<td>Estimate total daily dose need to achieve target $AUC_{24}$</td>
<td>$\text{New TDD} = \frac{\text{Current TDD} \times AUC_{0-24} \text{ (desired)}}{AUC_{0-24} \text{ (calculated)}}$</td>
</tr>
<tr>
<td>13</td>
<td>Calculate predicted steady state $C_{\text{max}}$ for new dosing regimen</td>
<td>$C_{\text{ss,max}} = \frac{\text{New dose}}{CL \times t} \times \frac{1-e^{-k \cdot \tau}}{1-e^{-k \cdot \tau_{\text{au}}}}$</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; $k_e$: elimination rate constant; $V_d$: volume of distribution; $C_t$: concentration at time $t$; (i.e. first of 2 levels drawn following dose); $C_d$: concentration at time $t_d$; (i.e. second of 2 levels drawn following dose) $t$: time at which $C_t$ is drawn, $t_d$: time at which $C_d$ is drawn. $\text{CL}_{\text{van}}$: vancomycin clearance. $\text{TDD}$: total daily dose. $\text{AUC}$: area under the concentration-time curve. $AUC_{24}$: 24 hour area under the concentration-time curve.