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/m²]
   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. Cockroft-Gault Equation

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

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></td>
</tr>
<tr>
<td>Trough-based protocol (IHD, PD, nocturnal CRRT, dose-by-level)</td>
<td></td>
</tr>
<tr>
<td>Continuous IV infusion</td>
<td>AUC 400 – 600 mg*h/L</td>
</tr>
<tr>
<td>Trough ~15 (10-20) mg/L</td>
<td>Trough-based protocol</td>
</tr>
<tr>
<td>Random 17-25 mg/L</td>
<td></td>
</tr>
<tr>
<td>Continuous IV infusion</td>
<td></td>
</tr>
</tbody>
</table>

Meningitis/ventriculitis (empiric or definitive)

<table>
<thead>
<tr>
<th>Trough-based protocol</th>
<th>Trough 15-20 mg/L</th>
</tr>
</thead>
</table>

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

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.

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

Obese (BMI ≥ 30) CrCL < 30 or AKI, IHD, CRRT, unavailable Scr in emergent situations (e.g. code sepsis or ED)

*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 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 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

<table>
<thead>
<tr>
<th>Expected target trough range correlating to AUC</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Individualized: select a 5-point range close to trough associated with therapeutic AUC (400-600 mg/L) | • 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. |
| See Excel calculator | Calculate lower (x) and upper (y) limits of target range using linear proportionality  
Option to calculate:  
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

<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;130</td>
<td>ICU only: 15mg/kg x1 (max 3g), then use PK calculator for daily dose given as continuous infusion</td>
<td>40-45 mg/kg</td>
<td>Random level 24 hours after start of infusion</td>
</tr>
<tr>
<td>&gt;90</td>
<td>15 mg/kg Q8-12H† Obsese: use PK calculator</td>
<td>30 – 45 mg/kg/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 Obsese: use PK calculator</td>
<td>20– 40 mg/kg/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 Obsese: use PK calculator</td>
<td>20 – 30 mg/kg/day</td>
<td>Q24H: Peak 1hr after 3rd / trough 30 min before 4th dose</td>
</tr>
</tbody>
</table>
| 10-29                         | 10 – 15 mg/kg Q24H to 15 mg/kg Q48H Obsese: 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 |
| <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  
Single pre-dialysis level (preferred)  
Alternative: single level 4 hours after completion of dialysis session |
| Hemodialysis                  | Initial: ~ 20-25 mg/kg x 1 (max 2gm)  
Maintenance: see appendix F | N/A | N/A |
| CRRT† or nocturnal CRRT       | Initial: 20-25 mg/kg x 1 (max 2gm)  
Maintenance: 10 – 15 mg/kg Q24H | N/A | N/A |
| Peritoneal dialysis           | 10 – 15 mg/kg IV x1, then dose by level  
Dosing for intraperitoneal (IP) instillation: see Lexioncom (NOT part of protocol) [Li 2016]  
Intermittent (1 exchange/day): 15-30mg/kg IP initially, then dose by level*  
Supplemental doses may be necessary for AKI patients | 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 CrCladj > 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

‡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

---

* AKI (based on KDIGO, RIFLE, AKIN classifications):
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.

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

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

- This AUC value applies to that calculated in a single dosing interval \(\Delta t\) \(\Rightarrow\) 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 H)

**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.

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

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.

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

**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 15-20**
Vancomycin Loading Dose
~20-25 mg/kg (max 2000mg)

---

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

<table>
<thead>
<tr>
<th>Augmented Renal Function</th>
<th>Loading Dose</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg/kg TBW [max 3000 mg]</td>
<td>Calculate 24 hour requirement using AUC dosing calculator (tab 1 on excel file) and start infusion based on this calculation (round to nearest 250 mg)</td>
<td></td>
</tr>
</tbody>
</table>

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
  o 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%
  o If subtherapeutic: increase the dose (see adjusting doses below) and recheck level in 24 hours
  o 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
  o 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)
  o If patients are sub-therapeutic or supra-therapeutic on intermittent dosing
    ▪ Dosing for continuous infusion should be calculated on a case to case basis using existing data.
    ▪ Can use SHC Vancomycin Dosing Calculator 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
H: PK Equations (same as those used in SHC Vancomycin Excel AUC Calculator)

AUC-based dosing: initial dosing
1. Step 1: estimate Cl\text{vanco} (L/hr) = ke \times Vd
   a. In general populations: Matzke Equation: ke = 0.00083 \times CrCl + 0.0044
   b. In obese patients: Crass et al 2018: Cl\text{vanco} = 9.656-0.078 \times \text{age} – 2.009 \times \text{SCr} + 1.09 \times \text{sex} + 0.04 \times TBW^{0.75}, where female = 0 and male = 1.
2. Step 2: estimate total daily dose = 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 ke 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_1}{e^{-k t}} ) where t = infusion time</td>
</tr>
<tr>
<td>5</td>
<td>Calculate true trough, ( C_{\text{min}} )</td>
<td>( C_{\text{min}} = C_{\text{max}} \times e^{-k e \times (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 t})}{t \times k e (C_{\text{max}} - C_{\text{min}} \times e^{-k t})} ) where t = infusion time</td>
</tr>
<tr>
<td>7</td>
<td>Calculate vancomycin clearance</td>
<td>( 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>Time for ( C_{\text{min}} ) 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 \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}{\text{tau}} )</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 t}}{1-e^{-k \text{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; \( \text{Tau} \): dosing interval; \( \text{Ke} \): elimination rate constant; \( \text{Vd} \): volume of distribution; \( \text{C}_1 \): concentration at time \( t_1 \) (i.e. first of 2 levels drawn following dose); \( \text{C}_2 \): 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 \( CL_{\text{van}} \): vancomycin clearance \( TDD \): total daily dose \( AUC \): area under the concentration-time curve \( AUC_{24} \): 24 hour area under the concentration-time curve
I: 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

<table>
<thead>
<tr>
<th>Description</th>
<th>Target trough range</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 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.  
Option to calculate:  
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
   Emily Mui, Pharm.D. BCPS: 08/2013

B. Gatekeeper
   Pharmacy Department

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

D. Review/Revision History:
   Lina Meng, Pharm.D., BCPS: 06/2015
   Janjri Desai, Pharm.D., MBA, BCPS: 10/2015, 03/2016, 08/2016
   Lina Meng, Pharm.D., BCPS, BCCCP: 08/2016, Emily Mui, Pharm.D., BCPS: 08/2016
   Calvin Diep, Liz Keil, Jamie Kuo, Lina Meng 5/2021, 1/2022

E. Approvals
   Pharmacy and Therapeutics Committee: 11/2015, 03/2016, 5/2021, 4/2022

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Stanford Health Care Stanford, CA 94305