Vancomycin Dosing Overview

I. Loading dose
   a. **Goal:** Provide loading doses to enhance the rapid obtainment of target vancomycin concentrations.
   b. **Data:** Appropriate early administration and adequate empiric antimicrobial therapy has been shown to decrease morbidity and mortality (e.g. sepsis; bacteremia; pneumonia). Seemingly this applies not only to drug selection, but also drug dosing. Aggressive dosing early in therapy may also decrease the development of resistance. Comparator outcomes data for vancomycin (LD vs. no LD) is very limited. Utilization of targeted interventions with computerized physician order entry (CPOE) has been shown to improve dosing with renally-eliminated antimicrobials. Guidelines suggest the use in “complicated infections” (Level of evidence: IIIB)
   c. **What to use:** Loading doses of **20-25 mg/kg** based on actual body weight (no adjustment for obesity) one time only doses. No adjustment for renal dysfunction.
   d. **When to use:** Loading doses may be used at the initiation of vancomycin for any indication, however, they are most likely to be clinically impactful in critically ill patients or those with severe invasive disease (e.g sepsis) and/or those with a deep-seated infection (e.g. osteomyelitis; endocarditis; meningitis; pneumonia).
   e. **Clinical Pearls:**
      i. Dose should be **20-25 mg/kg** – based on actual body weight. Maximum dose of 2,500mg
      ii. **No adjustment necessary for renal dysfunction** – maintenance dose will be scheduled at appropriate interval post-loading dose.
      iii. Follow rounding policy for specific loading dose calculation (e.g. if dose ≤ 2,000 mg round to nearest 250 mg; if dose >2,000 mg round to nearest 500 mg.
         1. If calculated loading dose is **>2,500 mg; dose should be capped at 2,500mg.** Given the extreme weight of the patient, contact ID/ASST PharmD pager (352-1322) for questions on further dosing modification.
      iv. **Hemodialysis:** Please refer to Table 1. (Vancomycin Dosing Frequency) for hemodialysis dosing.

II. Maintenance Dosing
   a. **Goal:** Maintain target trough concentrations at ranges to optimize bactericidal activity and clinical outcomes, while limiting toxicity and development of resistance.
   b. **Data:** Vancomycin dosing has evolved from historical target trough concentrations of 5-10 mcg/mL to current standards of a minimum of 10mcg/mL and 15-20 mcg/mL for invasive disease, seriously ill patients, and deep-seated infections (e.g. endocarditis; pneumonia; osteomyelitis; meningitis, etc.). Troughs still remain as the practical measure for clinical outcomes. Limited data suggests AUC/MIC ratios of ≥400 have been associated with better outcomes and bioactivity. Target troughs of 15-20 mcg/mL will correlate to an AUC/MIC ratio of 400 in most patients. Doses of 15-20mg/kg given every 8-12 hours will provide the appropriate trough concentrations for most patients. Utilization of targeted interventions with computerized physician order entry (CPOE) has been shown to improve dosing with renally-eliminated antimicrobials. Guidelines support these recommendations (Level of evidence: IIIB)
   c. **What to use:** Maintenance doses of **15mg/kg based on actual body weight** should be used in all patients. Although no specific adjustment for empiric dosing should be made, obese patients may require larger total daily doses at less frequent
intervals (Q8 hours). Dosing interval (see Table I) should be determined based on creatinine clearance, calculated with Cockcroft-Gault formula.

i. **Cockcroft-Gault** formula - **Ideal body weight** should be used in creatinine clearance calculation with the exception of obese patients (defined as >130% of ideal body weight). In obese patients an adjusted body weight [(ABW-IBW)*0.4 + IBW] should be used. Do not round serum creatinine values.

<table>
<thead>
<tr>
<th>CrCl (ml/min)*</th>
<th>Dosing Interval</th>
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<tbody>
<tr>
<td>≥ 70</td>
<td>Q8-12h</td>
</tr>
<tr>
<td>50 - 69</td>
<td>Q12H</td>
</tr>
<tr>
<td>30 - 49</td>
<td>Q24H</td>
</tr>
<tr>
<td>&lt; 30ml/min or &gt;1 mg/dL increase in SCr in last 24 hours</td>
<td>Initial loading dose of 15-20 mg/kg. Obtain vancomycin trough prior to second dose. Redose with 15 mg/kg when serum level ≤ 15 mg/L or when ≤ 20 mg/L in severe infections where penetration may be compromised (e.g., meningitis, pneumonia). May need to extend dosing interval to Q 48H.</td>
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</tbody>
</table>

**HEMODIALYSIS**

- ≥100kg:
  - Severe Infections (e.g., meningitis, pneumonia, osteomyelitis, endocarditis): 2 gm load then 1gm during last hour of each HD session.
  - Other Infections (e.g., UTI, SSTI, bacteremia): 2gm load then 750mg during last hour of HD.

- ≤100kg:
  - Severe Infections (e.g., meningitis, pneumonia, osteomyelitis, endocarditis): 2 gm load then 750mg during last hour of each HD session.
  - Other Infections (e.g., UTI, SSTI, bacteremia): 1 gm load then 500mg during last hour of HD.

**CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)**

(Maintain trough 10-15 mg/L or 15-20 mg/L in severe infections where penetration may be compromised (e.g., meningitis, pneumonia)

*Based on Cockcroft-Gault formula

**Clinical Pearls:**

i. Maintenance dose should be **15 mg/kg** in all patients (with the exception of hemodialysis-dependent patients) based on **actual body weight**.

ii. Frequency based on creatinine clearance calculated using the **Cockcroft-Gault** equation with **ideal body weight**, except in obese patients (use adjusted body weight or calculate without weight in formula).

iii. **Q8 hour** dosing interval should be avoided in patients ≥50 years of age

iv. In patients who received a loading dose, the maintenance dose should be scheduled at the next appropriate time for the determined dosing interval (see Table I above) following the conclusion of the loading dose

   1. Example: Loading dose received on (hospital day #1) HD 1 at 0800 – patient calculated to receive 1,500 mg Q12 hours – the maintenance dose should be scheduled for HD 1 at 2000 (12 hours after the loading dose)

v. Specific patient situations will arise where these guidelines may not be applicable (e.g. rapidly changing renal function; morbid obesity; amputees,
III. Dosing Rounding Policy
   a. All vancomycin orders of doses ≤ 2,000 grams should be rounded to the nearest 250mg increment (rounding up and down are both acceptable).
      i. Example: Calculated or electronically ordered dose of 1,815 mg should be rounded to 1,750 mg
   b. All vancomycin orders of doses > 2,000 grams should be rounded to the nearest 500mg increment.
      i. Example: Calculated or electronically ordered dose of 2,200 mg should be rounded to 2,000 mg
   c. If the electronic order received is for a dose that is not rounded, the verifying pharmacist should modify this order to represent the rounded dose.
   d. Max dose guidelines do apply. Single doses should not exceed 2,500 mg.
      i. Loading doses (20-25mg/kg) calculated at or above 2,500 mg should be capped at 2,500mg. (See Section I).
      ii. Maintenance doses (15 mg/kg) calculated at or above 2,500 mg should all be rounded to 2,500 as the max single dose and scheduled at the appropriate interval.

IV. Max Dose Guidelines
   a. Maximum doses of vancomycin should not exceed 2,500 mg.
   b. All maintenance doses (15 mg/kg) that exceed 2,500 mg will be rounded down to 2,500 mg and scheduled according to appropriate dosing interval. No supplemental dosing will be provided.
   c. Loading doses (20-25mg/kg) may often be calculated to exceed this 2,500 mg threshold. In these cases the following steps should be followed:
      i. Doses should be rounded to the nearest 500mg (See Section III)
         1. Doses > 2,500 mg should be capped at 2,500mg. Given the extreme weight of the patient, contact ID/ASST PharmD pager (352-1322) for questions on further dosing modification.

V. Monitoring Guidelines

Table I. Target Vancomycin Trough Concentrations

<table>
<thead>
<tr>
<th>Infectious Process</th>
<th>Target Trough Concentrations</th>
<th>TDM not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td></td>
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<tr>
<td>Uncomplicated SSTI (e.g. purulent cellulitis)a</td>
<td>10-15mcg/mLa</td>
<td></td>
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<tr>
<td>Complicated SSTI (e.g. diabetic foot infection; septic joint); endocarditis; osteomyelitisb; meningitisb; sepsis; bacteremia; pneumonia</td>
<td>15-20mcg/mL</td>
<td></td>
</tr>
</tbody>
</table>

aDe-escalation to alternative agents should be expedited in these infections, vancomycin monitoring is discouraged
bFor MRSA meningitis or MRSA osteomyelitis, concentrations of 20-25mcg/mL may be appropriate
Coagulase-negative Staphylococcal bacteremia = 10-15mcg/ml as target; if central venous catheter-related, short-course therapy of 5 days is sufficient and typically does not require vancomycin monitoring

a. **Optimal monitoring parameter** - Trough serum vancomycin concentrations are the most accurate and practical method for monitoring efficacy.

i. Trough concentrations should be obtained just prior to the next dose at steady state conditions (approximately the fourth dose).

ii. Minimum serum vancomycin trough concentrations should always be maintained above 10 mg/L to avoid development of resistance. For a pathogen with an MIC of 1 mg/L, the minimum trough concentration would have to be at least 15 mg/L to generate the target AUC:MIC of 400.

iii. Vancomycin serum trough concentrations of 15–20 mg/L are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes.

b. **Criteria for monitoring** - Trough monitoring is recommended for patients receiving aggressive dosing (i.e., to achieve sustained trough levels of 15–20 mg/L) and all patients at high risk of nephrotoxicity (e.g., patients receiving concurrent nephrotoxins).

i. Monitoring is also recommended for patients with unstable (i.e., deteriorating or significantly improving) renal function and those receiving prolonged courses of therapy (more than three to five days).

ii. Monitoring is NOT recommended if the anticipated course of therapy is ≤3-4 days or for urinary tract infections.

   a. Ex: Vancomycin is initiated in an uncomplicated SSTI and anticipated de-escalation to oral MRSA therapy will occur in 3-4 days; TDM is NOT recommended.

   b. Monitoring may not be necessary in patients receiving vancomycin for a Coagulase-negative Staphylococcus (CoNS) central line associated bacteremia. Vancomycin therapy is indicated for 5-7 days in these patients.

   c. Monitoring is not indicated in patients receiving oral vancomycin therapy.

c. **Frequency of monitoring** - Frequent monitoring (more than one trough before the fourth dose) for short course or lower intensity dosing (to attain target trough concentrations below 15 mg/L) is NOT recommended.

i. All patients on prolonged courses of vancomycin (exceeding three to five days) should have at least one steady-state trough concentration obtained no earlier than at steady state (prior to the fourth dose) and then repeated as deemed clinically appropriate.

   a. **TDM Caveat**: Drawing a vancomycin concentration prior to steady-state may be prudent if it allows for a pharmacist to better respond to the result. If drawn early (e.g., prior to 3rd dose), an adjustment should be made to account for added accumulation (roughly an additional 25% if obtained a full dosing interval prior to steady-state).

   b. There are limited data supporting the safety of sustained trough concentrations of 15–20 mg/L. Clinical judgment should guide the frequency of trough monitoring when the target trough is in this range. Once-weekly monitoring is recommended in hemodynamically stable patients. More frequent monitoring is advisable in patients who are hemodynamically unstable.

   c. An initial predialysis vancomycin level is recommended for patients receiving hemodialysis. Approximately 38% of vancomycin is removed...
during hemodialysis. Redose vancomycin if the predialysis level is <30 mg/dL. Patients receiving CRRT should have at least one steady-state trough concentration obtained (prior to the fourth dose) and then repeated as deemed clinically appropriate.

iv. Supplemental orders to “Hold if level >20” should NOT be written. This places increased responsibility upon nursing:
   a. 1.) The level must be drawn at an appropriate time by the nurse.
   b. 2.) The level must be appropriately interpreted by the nurse.
   c. 3.) Communication must take place among nurses between shifts and different units.
   d. “If.then” orders often result in delayed or missed doses. If there is a concern that current dosing may produce higher than expected levels, then the dose needs to be appropriately adjusted or the threshold for holding doses must be increased to >30mg/L.

VI. Continuous Infusion:
   a. Goal: To allow more rapid achievement of therapeutic drug concentrations than intermittent infusion; may optimize its bactericidal activity.
   b. Implementation: A loading dose of 20mg/kg (capped at 2,500mg) followed by an infusion at 1.25mg/kg/hr – 2mg/kg/hr (equivalent to 30-50mg/kg/day) based on total body weight.
      i. The loading dose should follow the same maximum (2,500mg) and rounding policies as previously explained.
      ii. Doses on the higher end (50mg/kg) should be considered for patients that are young (<25 years), obese, or hypercatabolic (e.g. burn patients).
      iii. The continuous infusion should be initiated at the conclusion of the loading dose.
   iv. Profiling Pearls:
      1. Choose the standard “Vancomycin Continuous Infusion 2500mg in 500ml NS (5mg/ml)”.
      2. Type infusion rate (ml/hr) in rate field.
      3. Type dose (in mg/kg/hr) in comment field.
      4. Expiration is 48 hours
      5. Place infusion on DEMAND and send first dose.
   c. Monitoring: A level should be drawn 12-16 hours after infusion started or dose is changed (“pseudo steady state”) to maintain serum vancomycin concentrations between 20-30mg/L depending on infection (e.g. deep-seated infections requiring higher end of dosing). Dose escalations and reductions based on levels should be adjusted according to the linear nature of the drug. Vancomycin concentrations >40mg/L should prompt a hold of the infusion for 4 hours and re-start at lower mg/hr rate. Data are inconclusive on the clinical benefit of continuous infusion regimens when compared with intermittent dosing.
      i. Repeat monitoring, once the patient is in goal range should only be done every 5-7 days, unless clinical condition necessitates earlier monitoring.

VII. Special Administration (Non-IV)
   a. Intrathecal administration
      i. Standard dose is 20mg IT daily
      ii. Consultation with ASST or infectious diseases is required
   b. Oral administration
      i. Standard dose is 125mg PO daily as vancomycin IV in oral solution
      ii. Please consult Clostridium difficile guidelines and treatment algorithm for indications
      iii. Consultation with ASST or infectious diseases is required
References:


