Vancomycin, a glycopeptide antibiotic with bactericidal activity against gram-positive infections, has been used clinically since the 1950s and has a wide therapeutic index. Since vancomycin exhibits concentration-independent killing, bacterial growth is inhibited as long as the unbound concentration is above the minimum inhibitory concentration (MIC) of the organism at the site of the infection. Vancomycin diffuses well into most body tissues, but distribution to lung tissue and the central nervous system is variable and dependent upon disease process. Lung penetration is suboptimal at routine doses and as a result higher serum concentrations are generally targeted in the treatment of pneumonia. Distribution into the cerebral spinal fluid is poor unless the meninges are inflamed. The inoculum size at the site of infection may also impact the activity of vancomycin. In vivo and mathematical models indicate that inoculum size may also have an impact on the efficacy of vancomycin.

Sparse data exist correlating efficacy and toxicity with vancomycin trough or peak concentrations. Historically, monitoring of vancomycin concentrations was minimized because pharmacokinetics are predictable and toxicity did not correlate with serum concentrations. Peak concentrations of vancomycin are of little value since bactericidal activity is independent of peak serum concentrations. Limited animal and human data indicate that the ratio of area under the curve (AUC) to MIC (AUC/MIC) is predictive of clinical outcome when treating methicillin-resistant Staphylococcus aureus (MRSA). Calculation of the AUC/MIC is cumbersome since it involves serial vancomycin concentrations; therefore, trough concentrations are recommended as a surrogate marker. Trough concentrations are drawn within 30 minutes of the next dose and should be maintained above 10 mcg/mL for uncomplicated infections and 15 to 20 mcg/mL for organisms with a MIC greater than 1 mcg/mL, hospital-acquired pneumonia, healthcare-associated pneumonia and ventilator associated pneumonia. The Infectious Diseases Society of America (ISDA) Guidelines for the Treatment of Endocarditis recommend trough concentrations of 10 to 15 mcg/mL; whereas, other guidelines specify target concentrations of 15 to 20 mcg/mL for S. aureus endocarditis. The 2004 ISDA Guidelines for Meningitis recommend trough concentrations of 15 to 20 mcg/mL with intermittent vancomycin dosing. Others have treated meningitis with a continuous infusion of high doses of vancomycin and targeting concentrations of 20 to 30 mcg/mL. Vancomycin Continuous Infusion for Meningitis

Prolonged and low exposure of vancomycin can select out resistant mutants and maintaining the sufficient concentrations throughout the dosing interval may prevent resistance. Some institutions have recognized a trend of increased MICs for vancomycin among S. aureus isolates, while others have noted a superior clinical response in treatment of MRSA pneumonia and bacteremia with lower vancomycin MICs. In January 2006 the Clinical and Laboratory Standards Institute established lower MIC breakpoints for S. aureus to improve detection of heterogeneously resistant isolates. Bacteremic patients with MRSA isolates with a MIC of 2 mcg/mL require a significantly longer treatment period and have a lower likelihood of bacterial eradication, and alternatives to vancomycin should be considered under these unusual circumstances. A trial of patients with MRSA bacteremia demonstrated higher rates of treatment failure with MICs ≥ 1 mcg/mL. Since low vancomycin concentrations are associated with increasing MICs, resistance and treatment failure of S. aureus, it is important to maintain trough concentrations greater than 10 mcg/mL. When first released in the 1950’s vancomycin was associated with nephrotoxicity. This was subsequently attributed to impurities in the product and after product purification the incidence was considered to be less than 5%. The occurrence of nephrotoxicity with vancomycin, however, increases when co-administered with aminoglycosides or furosemide. With increasing MIC concentrations, aggressive dosing and higher targeted trough concentrations, there is concern for an increased incidence of
nephrotoxicity. A retrospective cohort study determined nephrotoxicity, defined as an increase in serum creatinine of 0.5 mg/dL or 50%, was significantly higher in patients on four grams or more per day, with a total body weight of 101.4 kilograms or more, a creatinine clearance of 86.6 mL/min or less, or ICU status. Likewise, a recent retrospective cohort study of patients with health-care associated MRSA pneumonia demonstrated that nephrotoxicity is significantly higher with concurrent administration of nephrotoxic drugs, trough concentrations of 15 to 20 mcg/mL and treatment for greater than 8 days.

Similar to nephrotoxicity, ototoxicity was associated with initial product impurities and is rarely reported in the literature. It is somewhat elusive however, since it is more difficult to detect. Baseline and follow-up audiograms were used to detect high-frequency hearing loss in a case-controlled, retrospective analysis of patients with target vancomycin concentrations of 10 to 20 mcg/mL. Of the 89 patients, 11 (12%) experienced high-frequency hearing loss. Independent predictors were abnormal baseline audiograms and age over 53 years. Long-term follow up and correlation of trough vancomycin concentration were not evaluated in the study, but are important considerations.

Minimizing toxicity and resistance while improving outcomes is best accomplished by aggressive, empiric dosing based on renal function and actual body weight (table 1), tailoring therapy to MICs and monitoring vancomycin and creatinine concentrations. A loading dose of 20 to 25 mg/kg should be considered for critically ill patients in an effort to attain therapeutic concentrations quickly. Patients with pneumonia, meningitis, endocarditis, organisms with MIC ≥ 1 mcg/mL, sepsis, large volumes of distribution, body mass index ≥ 30 kg/m², prolonged therapy, renal insufficiency and dialysis require monitoring of trough concentrations to ensure adequate concentrations throughout the dosing interval and minimize toxicity.

Table 1. Adult vancomycin dosing nomogram

<table>
<thead>
<tr>
<th>Creatinine Clearance*</th>
<th>Initial Dose (ABW)†</th>
<th>Maintenance Dose(ABW)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥100 mL/min</td>
<td>15 - 25 mg/kg</td>
<td>10 mg/kg Q 8 h</td>
</tr>
<tr>
<td>80 - 99 mL/min</td>
<td>15 - 25 mg/kg</td>
<td>15 mg/kg Q 12 h</td>
</tr>
<tr>
<td>56 - 79 mL/min</td>
<td>15 - 25 mg/kg</td>
<td>10 mg/kg Q 12 h</td>
</tr>
<tr>
<td>40 - 55 mL/min</td>
<td>15 - 25 mg/kg</td>
<td>15 mg/kg Q 24h</td>
</tr>
<tr>
<td>30 - 39 mL/min</td>
<td>15 - 25 mg/kg</td>
<td>10 mg/kg Q 24h</td>
</tr>
<tr>
<td>20 - 29 mL/min</td>
<td>15 - 25 mg/kg</td>
<td>15 mg/kg Q 48 h</td>
</tr>
<tr>
<td>&lt;20 mL/min</td>
<td>15 - 20 mg/kg</td>
<td>Monitor serum concentrations</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>15 – 20 mg/kg or 1 g</td>
<td>500 - 750 mg after dialysis or monitor serum concentration as indicated in sections 7 below</td>
</tr>
<tr>
<td>CRRT</td>
<td>15 – 20 mg/kg</td>
<td>1 g Q 12 – 24 h Monitor serum concentrations</td>
</tr>
</tbody>
</table>

ABW – actual body weight, CRRT – continuous renal replacement therapy

* Dosing recommendations are based on decreasing creatinine clearance, which can be measured directly or estimated with equations such as the Cockcroft-Gault equation. In obese patients with a BMI > 30 kg/m², the Salazar-Corcoran equation is more precise and less biased. For more information; please consult the protocol for renal-based dose adjustments. Renal Function-Based Dose Adjustment in Adults

† Round doses down to the nearest 500 mg, 750 mg, 1 g, 1.25 g or 1.5 g dose. If higher single doses are calculated, then consider giving a smaller dose more frequently. Maximum infusion rate is 10 mg/min or over 1 hour, whichever is longer. Minimum dilution is 5 mg/mL in a peripheral line.
1. Patients with large volumes of distribution may require higher milligram per kilogram doses and serum concentrations are necessary to adjust doses as the volume of distribution changes. Initial loading doses of 20 to 25 mg/kg are useful to achieve and maintain therapeutic concentrations sooner. Patient conditions that can have larger volumes of distribution are sepsis, recent cardiac or trauma surgery, burns over 20% of the total body surface area or pregnancy. The usual volume of distribution varies from 0.4 to 1 liter/kg.

2. In patients with normal renal function the half-life ranges from 6 to 12 hours; as a result it can take up to 60 hours to reach steady state in patients with normal renal function and even longer in patients with renal compromise.

3. Trough concentrations are recommended for patients with aggressive dosing, targeting serum concentrations of 15 to 20 mcg/mL, obesity (BMI >30 kg/m²), at high risk for nephrotoxicity, with unstable renal function or on dialysis. Patients with rapidly changing renal function where vancomycin kinetics may be difficult to predict may be candidates for alternatives to vancomycin.

4. All patients receiving vancomycin therapy for prolonged therapy (at least 4 days) should have at least one steady-state concentration drawn. Concentrations should be drawn weekly on patients with stable hemodynamic and renal function and more frequently on unstable patients. Patients on more than 4 weeks of therapy can have a decrease in vancomycin clearance, thus it is important to monitor concentrations at this point in therapy. Infectious Disease guidance should strongly be considered for patients requiring more than 4 grams of vancomycin per day, and if the patient is on the Infectious Disease consult service, the ID attending physician should be consulted.

5. Target trough concentrations (within 30 minutes of the next dose):

<table>
<thead>
<tr>
<th>Treatment population</th>
<th>Desired Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>&gt; 10 mcg/mL</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>10 – 20 mcg/mL</td>
</tr>
<tr>
<td>An infection with a MIC ≥ 1 mcg/mL, hospital-acquired pneumonia, healthcare-associated pneumonia, ventilator-associated pneumonia, meningitis with intermittent dosing</td>
<td>15 – 20 mcg/mL</td>
</tr>
<tr>
<td>Meningitis, continuous infusion</td>
<td>20 – 30 mcg/mL</td>
</tr>
</tbody>
</table>

6. If a steady-state concentration is outside the target therapeutic range, then proportionate dosage adjustments should be made in 250-mg increments and/or consider changing the dosing interval.

7. High-flux hemodialysis (HD) is now the primary means of HD at UWHC and removes a significant amount of vancomycin. The average amount of vancomycin removed by high flux HD during a 3- to 4-hour session is 30 to 38%.

7.1. Most patients will require a vancomycin dose after each dialysis session. One method for dosing patients on a regular HD schedule (of three times per week) is to give an initial loading dose of 15 to 20 mg/kg and then empirically give 500 to 750 mg during the last hour of each HD session. If greater than three days of treatment is planned, then serum concentration monitoring is recommended.

7.2. A second method of dosing with HD is to draw a concentration 2 hours after the end of dialysis (to allow for vancomycin redistribution) and then give a supplemental dose to attain the desired target concentration.

7.3. Patients on a regular dialysis schedule will likely require the same dose of vancomycin after each dialysis session.
8. Continuous renal replacement therapy (CRRT) clears vancomycin more quickly than peritoneal or HD. Usually patients on CRRT require a vancomycin dose (1 g) every 12 to 24 hours and trough serum concentrations are used to ensure adequate dosing.49


Additional helpful references