

INTRAVENOUS VANCOMYCIN DOSING/MONITORING IN ADULTS

OBJECTIVE

This protocol is intended to maximize the appropriate use and to minimize toxicity and emergence of resistance associated with vancomycin. Vancomycin dosing based on the area under the curve to minimum inhibitory concentration (MIC), or AUC:MIC ratio, has been demonstrated to reflect clinical success for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The widely accepted practice of dosing based on vancomycin trough was promoted as a surrogate way to achieve target AUC:MIC ratios. Troughs do not necessarily correlate to the target AUC, however, and often result in AUCs that are higher than the demonstrated AUC toxicity threshold of 600mg.h/L. With the availability of online calculators and other technology, it is now more feasible to estimate the vancomycin AUC in regular clinical practice, making the use of the vancomycin trough to predict AUC unnecessary.

General Vancomycin PK/PD Principles

Volume of distribution:

- Hydrophilic molecule
- Vd 0.7 L/kg is used; use adjusted body weight if obese, (ranges from 0.4-1L/kg)
- In obese patients:
 - Vd in obese patients 0.3-0.8 L/Kg of actual body weight (ABW)
 - 30% of adipose tissue contains water
 - Additional weight is due to increased adipose tissue, muscle mass, and connective tissue
 - Hypoalbuminemia may result in elevated free vancomycin concentrations

EMPIRIC VANCOMYCIN DOSING FOR PATIENTS NOT ON DIALYSIS OR RENAL REPLACEMENT

- Dose based on actual body weight (ABW; including obese patients; max initial dose 2000mg)
- Loading dose (20-25mg/kg; max dose of 2000 mg) should be considered for the following situations:
 - Clinical instability
 - Documented MRSA infections
 - Suspected meningitis, endocarditis, or pneumonia
- Doses should be rounded to nearest 250 mg (e.g., 1000 mg, 1250 mg, 1500 mg, etc.)
- Maintenance dose and interval are based on renal function as determined by CrCl listed in Epic for clinically stable patients
- **Patients receiving vancomycin for surgical prophylaxis or group B strep prophylaxis are excluded from this empiric dosing guideline**

Creatinine Clearance (mL/min)	Initial Dose*
≥60	15 mg/kg Q12hr
~ 30-59	15-20 mg/kg 24hr
~ 21-29	15 mg/kg Q36hr
< 20**	15-20 mg/kg x 1 dose then dose by monitoring AUC

* Initial doses should be evaluated with consideration of the patient’s clinical picture, and evaluation with a pharmacokinetic calculator is encouraged

**See below for initial dosing for ARF, HD, PD, or CRRT patients

AUC-BASED VANCOMYCIN MONITORING

Guideline recommendations for AUC-based vancomycin dosing are for severe MRSA infections. The specific AUC targets for all vancomycin dosing will be used with the assumption that if a target that is validated for use in severe infections is achieved, it will also be adequate for less severe infections. Please keep this in mind when considering if dose adjustment is necessary, as a lower AUC may be adequate for less-severe or non-MRSA infections.

Most patients on vancomycin who require monitoring of levels will be monitored using AUC targets.

- **For patients with uncomplicated infection requiring ≤5 days of vancomycin therapy or receiving vancomycin for surgical prophylaxis, do not order levels unless treatment duration extends beyond 5 days. No monitoring required for short course therapy.**
- Empiric vancomycin should be discontinued if no indication for vancomycin therapy is identified within 72 hours of treatment initiation.

Exclusion Criteria:

See below for alternate dosing recommendations for patients with:

- acute renal failure
- intermittent hemodialysis
- peritoneal dialysis
- CRRT

Standard Dosing/Monitoring Procedure:

- One steady-state concentration (i.e., trough) will be obtained prior to the third or fourth dose
 - Patients with acute renal failure or hemodynamic instability may need a level earlier
- Calculate vancomycin AUC using the Epic Kinetics Navigator (See Kinetics Navigator User Guide)
- If hand calculation of AUC is needed, below are the calculations that will be used:

1. $V_d = 0.7L/kg * ABW$
 - a. (use adj body weight if >130% IBW; adj body weight = $IBW + 0.4[ABW-IBW]$)
2. $C = \text{Dose (mg; single dose)} / V_d$
3. Peak = vancomycin level + C (from above)
4. $K_{el} = [\ln(\text{peak}/\text{trough})] / \Delta\text{time}$
5. $CL = K_{el} \times V_d$
6. $AUC = \text{Dose (mg; in 24H period)} / CL$
 - a. Ex. 1000mg q12H = 2000mg in 24H period
7. For dose adjustment, a simple proportional method can be used (i.e. if calculated AUC was 900 with 3000mg/day, a dose of 1500mg/day approximately correlates to an AUC of 450)

Definitions:

- V_d = Volume of distribution (L)
- ABW = Actual body weight (kg)
- IBW = Ideal body weight (kg)
- C = Concentration (mg/L)
- K_{el} = elimination rate constant (hr^{-1})
- CL = clearance (L/hr)
- Δtime = time from start of infusion to level collection (hr)
- AUC = Area under the curve (mg.h/L)

- Ongoing monitoring and follow-up levels:
 - Stable patients
 - Recheck steady state trough every 5-7 days if the patient is clinically stable and renal function does not significantly fluctuate.
 - Special populations
 - For obese or elderly patients, there is a risk of accumulation of vancomycin.
 - Patients with a significant change in renal function ($\geq 50\%$ change or ≥ 0.3 mg/dL over 48 hr), clinical worsening, or hemodynamic instability may need earlier or more frequent levels per clinical judgment.

- For example, consider checking a trough initially prior to the 3rd or 4th dose and then every 3-4 days until no dose change has been required x 2 levels (at least 3-4 days apart). If stable, check once weekly while therapy is to be continued.
- Lab Monitoring
 - Check SCr at least twice per week if feasible (more frequently if patient is an inpatient).
 - The pharmacist may order labs (e.g., SCr) per this protocol as needed to assess the patient for vancomycin monitoring.
- If initial AUC is slightly below target, consider likelihood of accumulation of vancomycin in the patient prior to increasing dose.
- Dosing Pearls:
 - There is no demonstrated clinical benefit to a higher AUC if the patient is above 400 mg.h/L; there is no need to increase the dose if this threshold is met.
 - For non-severe infections, AUCs down to 350 mg.h/L have demonstrated efficacy.

Targets:

- The goal AUC/MIC ratio that should be targeted ranges between 400-600 mg.h/L
 - Assume MRSA MIC of 1 mcg/mL
 - MRSA MICs of 2 or greater must be verified by additional testing in lab; vancomycin is not the recommended agent for treatment if confirmed
- AUC greater than 650 mg.h/L can predict a higher risk of nephrotoxicity

DOSING IN ACUTE RENAL FAILURE OR INTERMITTENT HEMODIALYSIS

1. Give loading dose of 25 mg/kg x 1 dose (max 2 g)
2. Check a vancomycin level at 24-48 hours post-dose or with am labs on the day of the next hemodialysis session (if applicable) to obtain an estimated steady state level
 - a) High flux filters in HD will remove ~ 20-40% of the vancomycin dose during dialysis.
 - b) Pre-dialysis vancomycin levels will be used for assessment (if applicable)
3. Redose with 15 mg/kg x 1 when level approaches or drops below 10 mcg/dL; redosing at a higher level may be necessary depending on infection severity/clinical status of patient
4. Should a post-dialysis level be required, the post-dialysis level should not be drawn less than 4 hours after completion of the dialysis session to allow time for redistribution of vancomycin post-dialysis.

DOSING IN CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

1. Give initial loading dose of 20-25 mg/kg per actual body weight (max 2 g) for patients receiving conventional effluent rates of 20-25 mL/kg/hr for CRRT
2. Maintenance dose of 15-20 mg/kg q24 hours is recommended for effluent rates of 20-25 mL/kg/hr
3. Serum concentrations should be drawn early in therapy (e.g., prior to the 2nd or 3rd dose), and the dose should be adjusted to maintain target level of 10-15 mcg/dL
4. Keep in mind potential CVVH line clotting, which may interrupt elimination of the vancomycin during the dosing interval.

DOSING IN PERITONEAL DIALYSIS

1. Give 25 mg/kg x 1 dose (max 2 g)
2. Check a vancomycin level at about 48 hours post-dose and repeat level as needed

3. Redose with 15 mg/kg when level reaches 10-15mcg/dL or just below
4. Continue checking levels at estimated time repeat dose will be due based on prior intervals to determine need to redose
5. Caveats of vancomycin use in peritoneal dialysis:
 - For treatment of peritoneal dialysis-related peritonitis, intraperitoneal vancomycin is recommended instead of intravenous due to inadequate concentrations in peritoneal fluid with systemic administration
 - Achievement of therapeutic targets in patients on peritoneal dialysis is difficult without high trough levels. Consider use of alternative agent in critically ill patients requiring vancomycin therapy, if possible.

References

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