INTRAVENOUS VANCOMYCIN USE IN ADULTS

TABLE OF CONTENTS:

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Empiric vancomycin may be considered in high-risk patients to ensure adequate antibacterial coverage while awaiting culture results. The need to continue vancomycin, however, should be dependent on culture results confirming presence of an organism that requires vancomycin, such as methicillin-resistant *Staphylococcus aureus* (MRSA). Given the risk of toxicity with vancomycin, it should be discontinued as soon as clinical criteria no longer warrant its use. Current vancomycin dosing guidelines recommend targets specific to serious MRSA infections. These particular targets are not validated for non-MRSA infections, and lower targets are recommended for other types of infections in most situations. This guidance is intended to maximize the appropriateness of and minimize toxicity associated with vancomycin use.

VANCOMYCIN TARGETS AND RECOMMENDATIONS BY INDICATION

Guidance below reflects best practices when using vancomycin. Clinical context should be assessed to determine if vancomycin is needed and should be discontinued when not warranted given risk of toxicity. Data from the PROVIDE trial indicate that patients had better outcomes when AUC was <515 due to decreased toxicity observed.3 Further evidence from the CAMERA 2 study suggests that a 24-hour AUC of 470 or greater has been associated with increased toxicity, indicating lower AUCs may promote safety.4 Please keep these thresholds in mind when monitoring vancomycin therapy and adjusting doses. [See details and dosing pearls below in the Dosing and Monitoring Section]

TABLE 1: Vancomycin Recommended AUC Target by Indication

Clinical Scenario	Appropriate Use? (Y/N) If N, recommend D/C	Order levels* (Y/N)	Target AUC^	Recommendations
Bacteremia/Sepsis				
MRSA bacteremia, documented	Y	Y	350-515	ID consult highly recommended
Severe sepsis, unknown source	Y	N	N/A	If no MRSA isolated, discontinue vancomycin.
Confirmed GPC bacteremia (e.g., Streptococcus species, Enterococcus species, clinically significant coagulase-negative Staphylococcus species)	Y	Y	<515	-In cases of single positive blood culture with coag-neg Staph & high suspicion of contamination, vancomycin is generally not indicated and should be discontinued -Beta-lactams are the preferred treatment for GPC bacteremia when susceptible
Respiratory				
MRSA Pneumonia, documented	Y	Y	350-515	Consider switch to linezolid.
HAP/VAP, empiric	Y	N	N/A	Order MRSA nasal swab or evaluate BAL lower tract PCR panel if available; if negative for mecA, discontinue vancomycin.

Clinical Scenario	Appropriate Use? (Y/N) If N, recommend D/C	Order levels* (Y/N)	Target AUC^	Recommendations
CAP, empiric	Assess if high risk for MRSA using NM algorithm; if not high risk, vanco is not recommended.	N	N/A	Order MRSA nasal swab or BAL PCR; if negative, discontinue vancomycin.
Skin/Soft Tissue				
MRSA abscess, documented, or purulent cellulitis	Y	Y Levels may be indicated based on duration	<515	Increased association of MRSA with purulent cellulitis; discontinue vancomycin if MRSA wound PCR negative or if no MRSA isolated.
Non-purulent cellulitis	N		N/A	Vancomycin should not be used for non-purulent cellulitis. See NM skin/skin structure infection guidelines.
Bone/Joint				
MRSA osteomyelitis or joint infection	Y	Y	350-515	Vancomycin may be appropriate as empiric therapy in cases of high suspicion of Staph-related infections without positive cultures. Long-term vancomycin treatment may increase risk of nephrotoxicity, conservative AUC targets may reduce risk.
Central Nervous System (CNS)				
CNS infection, empiric	Y	Y	350-515	
Other (Note: Vancomycin rarely indicated in these scenarios)				
Intra-abdominal infection, empiric	N		N/A	Rare pathogen: MRSA not a significant cause of IAI. Reasonable to start if MRSA isolated. In rare situations where vancomycin is used, AUC <515 may promote reduced risk of toxicity.
Urinary tract infections/ Pyelonephritis	N		N/A	Rare pathogen: If MRSA isolated in urine in absence of urinary catheter (e.g., skin colonization), ID consult should be obtained to define source of organism. Blood cultures should be collected for surveillance of hematogenous spread. In rare situations where vancomycin is used, AUC <515 may promote reduced risk of toxicity.

*If levels are not indicated, they can still be monitored to avoid toxicity in a patient who requires ongoing vancomycin therapy or whose renal function is worsening (per the clinical judgement of the pharmacist).

^Clinical judgement should always be used in determining appropriate target AUC

VANCOMYCIN DOSING AND MONITORING

Pharmacy Protocol

All orders for vancomycin will automatically be dosed by pharmacy per this protocol or per the surgical prophylaxis dosing protocol based on indication. Pharmacists may order lab tests needed to monitor vancomycin appropriately including serum creatinine, vancomycin levels, and MRSA PCR screens.

General Vancomycin PK/PD Principles

Volume of distribution:

- Hydrophilic molecule
- Vd 0.7 L/kg is used; use adjusted body weight for Vd calculation if obese
- Vd is increased in patients with fluid overload (e.g., renal dysfunction, heart failure) and in inflammatory states (e.g., sepsis)

Empiric Dosing

- Dose based on actual body weight (ABW) for all patients, including those with obesity (max initial dose 2000 mg)
- Loading dose (20-25 mg/kg; max dose of 2000 mg) should be considered for the following situations:
  - Hemodynamic instability or critically ill, and ECMO patients
  - Documented severe MRSA infections
  - Suspected meningitis, endocarditis, or pneumonia
  - A loading dose is not recommended for hemodynamically stable patients or non-ICU patients
- Doses will be rounded to nearest 250 mg (e.g., 750 mg, 1000 mg, 1250 mg, 1500 mg, etc.)
- Maintenance dose and frequency are based on renal function as determined by creatinine clearance (CrCl) listed in Epic for clinically stable patients
- **Exclusions:**
  - Surgical or procedural (e.g., Group B Strep during delivery) prophylaxis
  - Acute renal failure (ARF)
  - Patients on renal replacement: hemodialysis (HD), peritoneal dialysis (PD), continuous renal replacement therapy (CRRT)

TABLE 2: Vancomycin Empiric Dosing

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

* Initial doses should be determined with consideration of the patient's clinical picture

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

Monitoring/Dose Adjustment Procedure

- The need for vancomycin should be assessed at initiation and daily to ensure appropriate usage.
- If anticipated vancomycin duration to exceed 72 hours, one steady-state concentration (usually a trough) will be obtained prior to the third or fourth dose. SEE TABLE 1 ABOVE FOR WHEN CONCENTRATION MONITORING IS RECOMMENDED. Check level prior to 3rd or 4th dose if indicated, otherwise if therapy goes longer than 5 days.
  - Patients with acute renal failure or hemodynamic instability may need a level earlier

- Calculate vancomycin area under the curve (AUC) using the Epic Kinetics Navigator (See Kinetics Navigator User Guide)
- Target AUC is per above TABLE 1 based on indication for vancomycin
- 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=Dose (mg; single dose) /Vd
3. Peak= vancomycin level + C (from above)
4. K_{el}= [ln(peak/trough)]/Δtime
5. CL= K_{el} x V_d
6. AUC= 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)

- A progress note assessing the vancomycin therapy will be entered into the patient chart for each vancomycin level that is ordered using the data pulled from the Epic Kinetics Navigator.

- Ongoing monitoring and follow-up levels:
    - Routine weekly concentration monitoring for patients with stable renal function IS NOT INDICATED.
    - Patients with a significant change in renal function (serum creatine [Scr] ≥ 50% change or ≥ 0.3 mg/dL over 48 hr), clinical worsening, or hemodynamic instability should have concentration monitoring undertaken.
    - Lab Monitoring
        - Check Scr at least twice per week if feasible (may be more frequently if patient is an inpatient).
        - The pharmacist may order labs (e.g., Scr, vancomycin levels, MRSA screens, etc.) per this protocol as needed to assess the patient for vancomycin monitoring.

- Dosing Pearls:
    - Assessing clinical response and applying clinical judgement should always guide therapy adjustments. AUC calculations are just another tool to help with this assessment and adjusting doses solely to achieve values in the "target range" in a clinically improving patient is not appropriate. It is important to remember that the calculated AUC is only an estimate, so making minor adjustments to the dose to achieve a small change in the AUC in a clinically stable patient is not necessary.
    - No minimum AUC threshold has been established for non-MRSA patients or patients with non-severe MRSA infection. If the AUC appears too low but patient is clinically stable, verify the patient is on a minimum dose of 15mg/kg with an appropriate, CrCl-based frequency per the initial dosing guidelines.
    - ECMO patients do not require special dosing outside of the usual additional care taken for management of critically ill patients including a loading dose and close monitoring of levels to ensure adequate exposure.

DOSING AND MONITORING IN RENAL FAILURE PATIENTS

Dosing in Acute Renal Failure

1. Give initial dose of 15 mg/kg x 1 dose (max 2000 mg).
2. The dosing pearls outlined above should always guide dose adjustments to ensure vancomycin is indicated and promote safety.
3. Check a vancomycin level at 24 to 48 hr post-dose; check subsequent levels based on expected need to redose.
4. Redose with 10 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.

Dosing in Hemodialysis

Vancomycin dosing in patients receiving hemodialysis (HD) is complex due to variable drug clearance due to individualized residual renal function along with different types and durations of HD. Robust evidence is lacking to support AUC-guided dosing strategies in HD, thus intermittent concentration monitoring is recommended to guide dosing.

1. **Initial dose:** 20 mg/kg actual body weight (max 2000 mg)
    a. If dose given prior to planned HD that day, consider administering 500 mg post-HD dose.
    b. Pre-HD concentration goal: ~15-22 mcg/ml

2. **Check pre-HD concentration** (e.g., level) prior to next scheduled HD session (e.g., initial vancomycin given, and one HD session has already occurred). Level may be ordered with AM labs on morning of second HD session.

Pre-HD Serum Concentration	Maintenance Vancomycin Dose* (to be given following HD)	Maximum Vancomycin Dose
> 22 mcg/mL	No additional dose required	No additional dose
15-22 mcg/mL	Give vancomycin 500 mg	500 mg
10-14.9 mcg/mL	Give vancomycin 5-7.5 mg/kg	750 mg
< 10 mcg/mL	Give vancomycin 10-15 mg/kg	1500 mg

*****Weight-based dosing recommended with dose rounding to account for inter-patient differences, particularly those with extreme body weights (e.g., underweight, obesity). Consider higher end of dosing range for more deep-seated, severe infections.

    a. Post-HD levels may be considered if needed based on patient's clinical status, residual renal function, infection severity, and/or variations in HD that may affect the level. If indicated, post-HD level should be drawn at least 4 to 6 hours after completion of HD session to account for redistribution of vancomycin. Post-HD Therapeutic Goal: 10-15 mcg/ml if checked. Redose as indicated to maintain this level.

3. **Maintenance dose:** Should be given following HD session, guided by pre-HD concentration as shown in table above with general guidance of ~5-10 mg/kg supplemental doses post-HD, targeting pre-HD goal concentration.

4. Continued Monitoring:
    a. For patients on stable, scheduled HD regimens (e.g., daily OR three times weekly) who have in-range pre-HD vancomycin level, may check less frequently (e.g., weekly or every other week) as long as HD settings remain unchanged and no concern for related adverse effects or clinical worsening.
    b. For patients on varying HD schedules or those with out-of-range pre-HD vancomycin levels, recommend checking level prior to next dialysis session to inform maintenance dose.
    c. If HD session must be stopped early or interruptions occur, a planned maintenance dose may need to be held or adjusted due to reduced vancomycin clearance. Consider evaluating need via level monitoring.

Dosing in Continuous Renal Replacement Therapy

1. Give initial dose of 20-25 mg/kg per actual body weight (max 2000 mg).
2. Maintenance dose of 10-15 mg/kg q24 hours is recommended for dialysate/ultrafiltration rates up to 4 L/hr total.
    - For rates over 4 L/hr, consider contacting your ADSP pharmacist to discuss dosing.
3. Serum concentrations should be drawn early in therapy when indicated (e.g., prior to the 2nd or 3rd dose), and the dose should be adjusted to maintain target level of 10-20 mcg/dL depending on infection severity.
4. Keep in mind potential CRRT line clotting and rate changes, which may interrupt or alter elimination of the vancomycin during the dosing interval.

Dosing in Peritoneal Dialysis

1. If a patient is receiving vancomycin intraperitoneally, please refer to the Intraperitoneal Antibiotic Dosing Protocol.
    - For treatment of peritoneal dialysis-related peritonitis, intraperitoneal vancomycin is preferred due to inadequate concentrations in peritoneal fluid with IV administration.
    - Systemic infections may be treated with intraperitoneal vancomycin if therapeutic levels are achieved.
    - For patients with hemodynamic instability or deep-seated (e.g., CNS) infections, may consider IV administration.
2. Intravenous (IV) vancomycin dosing, when indicated:
    - Give 20 mg/kg x 1 dose IV (max 2000 mg).
    - Check a vancomycin level at about 48 hours post-dose and repeat level as needed.
    - Redose with 15 mg/kg when level reaches 10-15mcg/dL or just below (about every 5-7 days, usually)
    - Continue checking levels at estimated time repeat dose will be due based on prior intervals to determine need to redose.

References

1. Rybak M, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm* 2020; 77:835-64. DOI: 10.1093/ajhp/zxaa036.
2. Moise PA, Forrest A, Bhavnani SM, et al. Area under the inhibitory curve and a pneumonia scoring system for predicting outcomes of vancomycin therapy for respiratory infections by Staphylococcus aureus. *AJHP* 2000; 57(suppl 2):1079-2082. DOI: 10.1093/ajhp/57.suppl_2.S4
3. Moise-Broder PA, Forrest A, Brimingham MC, et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. *Clin Pharmacokinet* 2004; 43(13):925-42. DOI: 10.2165/00003088-200443130-00005.
4. Hong J, Krop LC, Johns T, et al. Individualized vancomycin dosing in obese patients: a two-sample measurement approach improves target attainment. *Pharmacotherapy*. 2015(35):455-63. DOI: 10.1002/phar.1588.
5. Lodise TP, Rosenkranz SL, Finnemeyer M, et al. The emperor's new clothes : Prospective observational evaluation of the association between initial vancomycin exposure and failure rates among adult hospitalized patients with methicillin-resistant Staphylococcus aureus bloodstream infections (PROVIDE). *Clin Infect Dis* 2020; 70(8):1536-45. DOI: 10.1093/cid/ciz460.
6. Liu J, Tong SYC, Davis JS, et al. Vancomycin exposure and acute kidney injury outcome: a snapshot for the CAMERA2 study. *Open Forum Infect Dis* 2020; 7(12):ofaa538. DOI: 10.1093/ofid/ofaa538.
7. Drew RH and Sakoulas G. (2018) Vancomycin: Parenteral dosing, monitoring, and adverse effects in adults. In Hooper DC (ed.) *UpToDate*. Retrieved February 14, 2019 from https://www-uptodate-com.mwu.idm.oclc.org/contents/vancomycin-parenteral-dosing-monitoring-and-adverse-effects-in-adults.
8. Cardone KE, Chen WZ, Grabe DW, et al. Evaluation of the pharmacodynamic profile of commonly used intravenous vancomycin dosing schemes in patients on automated peritoneal dialysis. *J Antimicrob Chemother* 2014; 69:1873-6. DOI: 10.1093/jac/dku081.
9. Crew P, Heintz SJ, Heintz BH. Vancomycin dosing and monitoring for patients with end-stage renal disease receiving intermittent hemodialysis. *AJHP* 2015; 72:1856-64. DOI: 10.2146/ajhp150051.