

**Vancomycin Area Under the Curve (AUC) Dosing Guideline**

**Template for Institution Adaptation**

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Contents

[**Background of AUC-Guided Vancomycin Dosing** 4](#_Toc63242821)

[**Determining the Vancomycin Dosing Strategy** 5](#_Toc63242822)

[Assessment of patient weight and renal function 5](#_Toc63242823)

[Vancomycin Loading Doses 7](#_Toc63242824)

[Vancomycin AUC-Guided Dosing & Monitoring 7](#_Toc63242825)

[Vancomycin Trough Guided Dosing and Monitoring 11](#_Toc63242826)

[**Vancomycin Dosing in Special Populations** 13](#_Toc63242827)

[Patients with renal insufficiency requiring dialysis 13](#_Toc63242828)

[References: 16](#_Toc63242829)

[Appendices 17](#_Toc63242830)

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# **Background of AUC-Guided Vancomycin Dosing**

Vancomycin is a glycopeptide antibiotic used for empiric and definitive treatment of gram-positive infections, including methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin requires therapeutic drug monitoring due to its narrow therapeutic index. The vancomycin pharmacokinetic/pharmacodynamic (PK/PD) parameter best correlated with efficacy is area under the curve (AUC) to minimum inhibitory concentration (MIC). Clinical evidence suggests an AUC/MIC greater than 400 mcg\*h/mL decreases treatment failure, especially when this threshold is reached within the first 24-48 hours of therapy for deep-seated and severe methicillin-resistant *S. aureus* (MRSA) infections (Lodise 2014). Trough concentrations were previously used as surrogates for AUC > 400 mcg\*h/mL; however, troughs accurately predicted a patient’s AUC only 75% of the time and frequently led to supratherapeutic AUCs. Instead, calculating AUC based on first-order PK equations or with Bayesian modeling may accurately predict a patient’s true AUC over 97% of the time (Neely 2014). Furthermore, trough concentrations greater than 15 mcg/mL are correlated with increased vancomycin-associated acute kidney injury (AKI) (Bosso 2011; van Hal SJ 2013). When using AUC-based dosing, AUC values less than ~600 mcg\*h/mL are associated with decreased rates of acute kidney injury (Aljefri DM 2019, Suzuki Y 2012). For this reason, consensus guidelines now recommend AUC-dosing and monitoring of vancomycin as the preferred approach to achieve clinical efficacy and improve safety (Rybak 2020).

**Implementation Considerations:**

Each institution should address the following when adapting this guideline for local use:

If this is to be adapted as a protocol for pharmacists to dose and manage, how will the protocol be initiated and who can execute the protocol?

What patient populations will be included and excluded from protocol?

What are the requirements for pharmacist documentation of dosing and monitoring?

How will pharmacists be notified of vancomycin dosing consults?

How are consults terminated?

1. What are patient conditions that should be reported to prescriber/consultant even if within protocol?

# **Determining the Vancomycin Dosing Strategy**

## Assessment of patient weight and renal function

* Weight: Use actual/total body weight (TBW)
* Renal function: Calculate Creatinine Clearance using Cockcroft-Gault (CG) equation
	+ Serum creatinine values less than 1 mg/dL will greatly elevate the calculated creatinine clearance. This is especially true for elderly patients, malnourished patients, and spinal cord injury patients. These populations have reduced muscle mass as a fraction of total body weight and so may generate less creatinine. Although some literature recommends using a minimum of 1 mg/dL in this population, this may underestimate clearance and result in sub-therapeutic dosing.
	+ Cockcroft-Gault has been validated in patients with stable renal function but is not a great tool in patients with fluctuating renal function. If a patient has a substantial increase or decrease in SCr, the patient’s renal function is *at best* what is calculated by the CG equation. Clinical judgment should be exercised to best approximate renal function in the setting of rapid fluctuations in SCr; urine output may be a useful surrogate marker in these settings.
	+ Note that the controversy of what weight (if any) is best to use in the CG equation is still unresolved (*Ann Pharmacother* 2013; 47:1039; *Am J Health Syst Pharm* 1997; 54:2505; *Pharmacotherapy* 2011; 31:658)).
		- If using weight in calculations, the use of actual body weight in obese patients will overestimate creatinine clearance and the use of ideal body weight (IBW) will underestimate creatinine clearance. Consequently, adjusted body weight (ABW) can be considered if a patient’s weight is more than 30% over the ideal body weight (ABW = IBW + 0.4 (TBW-IBW)).
* Ultimately – the strategy for estimating and monitoring a patient’s renal function should be based on institution-specific practice
* If using Bayesian software programs, your institution should work with the software company to determine the best variables and restriction parameters to put on CrCl calculations within the software. Things like creatinine rounding, max cut offs (e.g., 150 mL/min), and which weight to use can be custom programmed at each institution.

Vancomycin Dosing Targets:

|  |  |
| --- | --- |
| **Indication** | **Vancomycin Dosing** |
| **Suspected or confirmed *Staphylococcus aureu*s**Bacteremia (all sources)EndocarditisMeningitis/CNS infectionOsteomyelitisNecrotizing fasciitisPneumoniaEmpiric therapy for fever and neutropeniaSepsis, source unknownSkin/soft tissue infection  | Target AUC24 400-600 mcg\*h/mL  |
| Other organisms (non-*S. aureus*) | [Institution-specific decision point to utilize AUC guidance for all vancomycin dosing compared to a mix of AUC or trough pending organism]Target trough (~10-15 mcg/mL likely adequate) or AUC guided as above (<600 mcg\*h/mL)Of note - there is some data suggesting an AUC target of 380-400 for Enterococcal infections (Jumah 2017). AUC-guided dosing may still be preferred for patients on prolonged courses of vancomycin or with multiple risk factors for nephrotoxicity. |
| Surgical Prophylaxis | As per local Antimicrobial Prophylaxis for Surgical Procedures ProtocolExample:≤70 kg – 1 gm IV71 – 109 kg – 1.5 gm IV>110 kg – 2 gm IV |
|  |

## **Vancomycin Loading Doses**

* Loading doses are recommended for patients with sepsis and patients with suspected CNS infections at minimum. Loading doses can be considered for any serious infection (e.g., endocarditis).
* For simplicity, a weight-based strategy of 25 mg/kg is advocated for the loading dose.
* A 20 mg/kg loading dose instead of a 25 mg/kg loading dose should be considered for patients with renal dysfunction, including patients with AKI, patients on renal replacement therapy (e.g., CRRT, HD, PD), and with other end organ replacement therapy (e.g., Molecular Adsorbent Recirculating System (MARS)). Maximum individual doses should be determined locally; the guidelines recommend a maximum 3 gm for loading doses. *EXAMPLE* table provided below.
* The loading dose is considered the first dose

|  |  |  |
| --- | --- | --- |
| **Patient Weight** | **Standard Loading Dose (~25 mg/kg total body weight)** | **Modified Loading Dose (20-25 mg/kg total body weight)***Obese (BMI ≥30), CrCl <30 mL/min or AKI, IHD, CRRT, unavailable SCr in emergent situation* |
| 36-45 kg | 1,000 mg x 1 | 750 mg x 1 |
| 46-55 kg  | 1,250 mg x 1 | 1,000 mg x 1 |
| 56-65 kg | 1,500 mg x 1 | 1,250 mg x 1 |
| 66-75 kg | 1,750 mg x 1 | 1,500 mg x 1 |
| 76-120 kg | 2,000 mg x 1 | 1,750 mg x 1 |
| >120 kg | 2,000 – 3,000 mg x 1 | 2,000 mg x 1 |
| Time maintenance doses to start based on renal function/planned dosing interval (e.g., wait 24 hours to start maintenance regimen if CrCl = 30 and maintenance dosing interval q24h).  |

## **Vancomycin AUC-Guided Dosing & Monitoring**

* + Empiric AUC-Guided Dosing
		- Vancomycin doses should be calculated to target an AUC24 of ≥400 mcg\*h/mL (ideal range 400-600 mcg\*h/mL).
		- Two strategies - First Order Equations and Bayesian
	+ Initial patient-specific dosing recommendations can be made using first-order equations based on population-PK to determine an initial starting dose (Appendix 1)
	+ Initial patient specific dosing recommendations using Bayesian software will be based on patient specific factors (e.g., age, gender, height, weight, SCr) inputted into a population PK model. Depending on the Bayesian software program used, the population model is different and may be able to be modified with each new patient (i.e., some programs allow you to pick from more than one model).
* Vancomycin can also be given as a continuous infusion.
	+ Starting a patient on CI vancomycin
		- Based on currently available data, a loading dose of 15 to 20 mg/kg, followed by daily maintenance CI of 30 to 40 mg/kg (up to 60 mg/kg) to achieve a target steady-state concentration of 20 to 25 mcg/mL (AUC of 480-600)
	+ **Therapeutic Drug Monitoring - First Order Equations**
		- AUC24 can be accurately calculated based on individual PK parameters derived from 2 appropriately timed serum concentrations. When drawing 2 levels, both levels should be drawn following the same dose with the first level being drawn approximately 2 hours after the completion of the infusion (to allow for the completion of the infusion and distribution) and the second level drawn at least 1 half-life after the first level. Levels should be drawn with ≥1 half-lives between each level (a *minimum* of 4 hours). If drawn too close together, the calculated ke will be less accurate leading to downstream calculation errors.
		- Two levels may be considered after the initial dose (“First-dose levels”) in patients where population PK equations may not accurately identify clearance (e.g., elderly, obese, septic) and for indications where early vancomycin optimization is important (e.g., bacteremia, endocarditis). First-dose levels are not indicated for patients where anticipated duration of vancomycin is <48 hours (e.g., surgical prophylaxis, skin and soft tissue infections in patients on observation) or in situations where they cannot practically be drawn (e.g., patients going to the OR).
			* Note: First-order equations with two levels are less accurate than Bayesian modeling, particularly when patients are not at steady state
		- When first-dose levels are checked, a repeat AUC evaluation is recommended at steady state on or around the 4th dose as the patient’s clinical condition can change dramatically early in the course of therapy (e.g., with fluid resuscitation). In certain situations (e.g., for anticipated short courses of therapy or in stable patients), a steady-state trough can be checked on or around the 4th dose instead.
		- If 2 levels have not been checked after the initial dose, 2 levels should be checked once concentrations are near steady-state (on or around the 4th dose, or after the 3rd dose if the patient received a loading dose) if vancomycin is to be continued.
* What if 2 concentrations were ordered but only 1 was drawn?
* If the patient was not at steady state, such as after the first dose, then 2 repeat concentrations must be re-ordered. You cannot repeat only 1 concentration off a new dose and use it in conjunction with the first level that was obtained after the previous dose. The two concentrations fall on different concentration time curves since the patient has not reached steady state.
* If the patient is at estimated steady state and the second level was collected as a trough (e.g., 30-60 minutes prior to the next dose) it can be interpreted as a trough to guide the need for immediate dose changes. A second concentration (e.g., draw a midpoint level after the next dose) can be done to use with the previous concentration to complete the AUC calculations.
	+ **Therapeutic Drug Monitoring - Bayesian**
		- Bayesian software programs can be integrated into the EHR or accessed via a web-based application. For the latter, pharmacists will have to transcribe data from the EHR into the software platform.
			* In settings where pharmacists are transcribing data, institutions may choose to not enter certain patient populations into the software and using traditional dosing strategies instead (e.g., patients requiring renal replacement therapy)
		- One or two vancomycin concentrations can be checked after the first vancomycin dose. Drawing two levels initially to estimate AUC24 is recommended in obesity and critical illness, or in patients that may not “fit” the population model. The timing of the concentrations will depend on the software used. Some software can recommend the optimal time to check the concentration that would give the most informative patient specific vancomycin clearance. The benefit of using Bayesian software is that the timing of the concentrations is flexible.
		- If one vancomycin concentration is recommended, a reasonable time to draw the concentration is a random level after the first vancomycin dose or at steady state.
		- If two vancomycin concentrations are recommended, a reasonable time to draw the concentration is a peak and a trough in the same dosing interval after the first vancomycin dose or at steady state.
		- Once the concentrations are inputted into the software, the 24h AUC can be estimated for every 24h period until steady state is reached.
		- Bayesian software can provide a dosing regimen to achieve a specific AUC24 based on patient specific parameters. From there, the pharmacist can test different dosing regimens and the estimated AUC24 that would achieve the desired target.
		- If vancomycin dose changes are needed, one or two vancomycin concentration(s) can be checked within 48h after the new dose is implemented to estimate the new 24h AUC.
		- Once therapeutic AUC24 is reached, additional checks for vancomycin concentrations are based on institutional preference. General guidance is to re-check vancomycin concentration(s) if there is an acute change in the clinical status or renal function of the patient, and at a minimum every 5-7 days.
			* Programs starting new with pharmacy-to-dose or high rates of baseline AKI may wish to be more conservative and require two therapeutic AUCs without a dose change, checked 3-5 days apart, before transitioning to weekly monitoring
			* Patients on every 8-hour dosing may require more frequent monitoring
* If no regimen is identified via the Bayesian software model reference table, use the “custom dose” section to design a regimen

**Regardless of Monitoring Strategy:**

* + Conversion from AUC to Trough-Based Dosing or dosing guided by ‘random levels’ should be done for patients who develop acute kidney injury or new onset renal replacement therapy
	+ If trough/second-AUC levels are high, the adjusted regimen should be timed to allow drug clearance before re-dosing.

**Therapeutic Drug Monitoring - Continuous Infusion (CI)**

* AUC-based monitoring via CI vancomycin
	+ A single vancomycin serum level should be collected at steady-state
		- Can be collected at any time point during CI
	+ Collect blood sample via catheter lumen after a normal saline flush
		- Utilize lumen that vancomycin is NOT infusing through
	+ General serum level range for CI vancomycin
		- 20-25 mcg/mL
	+ Multiply serum vancomycin level by a factor of 24 to calculate AUC24
		- Ex: vancomycin serum level = 21 mcg/mL
			1. Multiply 21 mcg/mL \* 24
			2. AUC = 504 mcg\*h/mL
	+ If therapeutic: recheck level ~72-96 hours, sooner if renal function changes
	+ If subtherapeutic adjust based on proportional calculation assuming renal function is stable: 
	+ If supratherapeutic:

|  |  |  |
| --- | --- | --- |
| Vancomycin Concentration 25-30 | Vancomycin concentration 30-35 | Vancomycin concentration 35-40 |
| Hold infusion for 2 hours; decrease daily dose by 250-500 mg | Hold infusion for 3 hours; decrease daily dose by 500-750 mg | Hold infusion for 4 hours, decrease daily dose by 750 mg-1000 mg |
| Check dose reduction calculations with the proportional calculation above to ensure appropriate adjustments |

* Transitioning a patient from intermittent infusion to CI vancomycin
	+ Combine total daily vancomycin dose
		- Ex: Patient is receiving vancomycin 1500 mg IV q12h
			1. Transition to CI would be 3000 mg over 24 hour infusion
		- Some suggest lowering the total daily dose when converting to CI; however, this is institution specific
* CI vancomycin has predominantly been studied among hospitalized patients who are critically ill and patients in the outpatient setting as part of outpatient parenteral antimicrobial therapy programs
* CI has potential advantages (Hao 2016, Ma 2020)
	+ Previously demonstrated reduced or similar risk of nephrotoxicity compared to intermittent infusion vancomycin targeting trough goals of 15-20 mg/L with similar clinical efficacy
	+ Serum levels less dependent on sampling time (blood samples can be collected at any time point during infusion)
		- Less risk for timing errors for appropriate interpretation, particularly impactful in the outpatient setting
	+ Dose adjustments can be made by changing infusion rate of 24-hour infusion
	+ Simple and convenient method for AUC calculation, particularly in the outpatient setting where two-point PK is logistically challenging and for institutions who may not have Bayesian software readily available
* CI has potential disadvantages
	+ Patients are required to be connected to infusion device for 24-hours; however, beta-lactams such as oxacillin/nafcillin, penicillin G, piperacillin-tazobactam, etc. are frequently infused via this strategy
	+ Patients require a double lumen peripherally inserted central catheter (PICC) line or central venous catheter to allow vancomycin to be infused via one lumen and the blood sample to be collected via the other sample
		- Lumen should be flushed with normal saline prior to blood sample collection
		- Education required to ensure blood sample is not collected from lumen infusing vancomycin, which leads to inaccurate vancomycin levels
		- Check for potential incompatibilities with other drugs via y-site infusion (e.g., piperacillin-tazobactam)

## **Vancomycin Trough Guided Dosing and Monitoring**

* 1-level (trough concentration only) remains the preferred TDM strategy in certain scenarios to:
	+ Balance the potential burden of widespread 2-level monitoring
	+ Acknowledge the broad clinical experience with trough only monitoring
	+ Patients who have vascular access issues
	+ Other patient care factors where the collection of 2-AUC levels would be challenging or not in the best interest of the care team (e.g., Covid-19 positive patients)
* Considerations for 1-level monitoring:
	+ Infection site
		- Mild/Moderate skin and soft tissue infection with anticipated early PO switch
		- Intra-abdominal infection with source control
		- Urinary tract infection
	+ Confirmed or suspected non-MRSA infections (institution-specific decision)
	+ Renal function (See recommendations in next section)
		- Acute kidney impairment
		- Intermittent hemodialysis
		- Peritoneal dialysis
		- Continuous renal replacement therapy
* Dose adjustments can be made based on current institutional guidelines using proportion method or guidance tables such as the on below.

**EXAMPLE Interpretation of vancomycin levels and dose adjustment guide**

|  |  |
| --- | --- |
| Trough level | Recommended Action |
| < 10 mcg/mL | If goal is 10-15 mg/L, increase dose by 250 mgIf goal is 15-20 mg/L, increase dose frequency by one level (e.g., q24h to q12h) |
| 10 - 15 mcg/mL | If goal is 10 -15 mcg/mL: No change necessaryIf goal is 15 – 20 mcg/mL: Increase dose by 250 mg |
| 15 - 20 mcg/mL | If goal is 10 -15 mcg/mL: Decrease dose by 250 mgIf goal is 15 – 20 mcg/mL: No change necessary |
| 21 - 25 mcg/mL | If goal is 10 -15 mcg/mL: Decrease frequency by one level (e.g., q12h to q24h)If goal is 15 – 20 mcg/mL: Decrease dose by 250 mg |
| > 25 mcg/mL | Hold doseUse pharmacokinetic equations to estimate when concentration will be <20 mcg/mL to re-start new dosing regimen and/or check a random level and re-dose when concentration is <20 mcg/mL |

**Other Lab Monitoring**

* SCr should be checked every 72 hours, at a minimum.
* Daily SCr will be checked if the patient experiences a change in SCr ≥0.3 mg/dL or ≥50% increase from baseline or last value within 24-48 hours, is oliguric, has a new requirement for renal replacement therapy, or for any other safety concerns
* CBC with diff should be checked weekly, at a minimum.

# **Vancomycin Dosing in Special Populations**

## **Patients with renal insufficiency requiring dialysis**

*Intermittent Hemodialysis*

* Clinical judgment should guide the exact dosing, frequency and monitoring of therapy
* Routine vancomycin levels prior to or after each dialysis session are NOT necessary and are strongly discouraged.
* Approximately 30% of vancomycin is removed during a full 4-hour hemodialysis session and can be used an estimate to predict an approximate post-hemodialysis vancomycin concentration
* Consider scheduling vancomycin among patients with stage 5 chronic kidney disease with limited intrinsic renal function receiving a stable thrice weekly dialysis regimen (e.g. MWF or TTS).
* Consider obtaining random pre-dialysis vancomycin level with am labs the day of every third HD session (can be collected with AM labs to minimize the number of blood draws)
* An \*example\* dosing algorithm is provided below (adapted from Lewis SJ, Mueller BA. J Clin Pharmacol 2020, doi:10.1002/jcph.1727 and Zelenitsky SA et al. Clin Infect Dis 2012;55(4):527-33.)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Actual Body Weight** | **Loading Dose****(LD)^** | **Maintenance Dose****(MD)****48hr interval****(e.g., Mon/Wed OR Tues/Thurs)** | **Maintenance Dose****(MD)****72 hr interval****(e.g., Fri OR Sat)** | **Vancomycin Plasma Concentration****(Pre-dialysis AM random level on each 3rd HD session)** | **Dosage Adjustments****\*250 mg increase in dose if given over 72 hr interval** |
| < 70kg | 1750 mg  | 500 mg after HD | 750 mg after HD |

|  |
| --- |
| Cp < 10 mcg/mL |
| Cp 10-14.9 mcg/mL |
| Cp 15-19.9 mcg/mL |
| Cp 20-24.9 mcg/mL |
| Cp 25-30 mcg/mL |
| Cp >30 mcg/mL |

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| --- |
| 1000mg after each HD |
| 750mg after each HD |
| Continue current MD regimen |
| Continue current MD regimen |
| Decrease dose by 250mg |
| Hold Vancomycin  |

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| 70-90.9kg | 2000 mg  | 750mg after HD | 1000 mg after HD |

|  |
| --- |
| Cp < 10 mcg/mL |
| Cp 10-14.9 mcg/mL |
| Cp 15-19.9 mcg/mL |
| Cp 20-24.9 mcg/mL |
| Cp 25-30 mcg/mL |
| Cp >30 mcg/mL |

 |

|  |
| --- |
| 1000mg after each HD |
| 1000mg after each HD |
| Continue current MD regimen |
| Continue current MD regimen |
| Decrease dose by 250mg |
| Hold Vancomycin  |

 |
| 91-110.9kg | 2250 mg | 750mg after HD | 1000 mg after HD |

|  |
| --- |
| Cp < 10 mcg/mL |
| Cp 10-14.9 mcg/mL |
| Cp 15-19.9 mcg/mL |
| Cp 20-24.9 mcg/mL |
| Cp 25-30 mcg/mL |
| Cp >30 mcg/mL |

 |

|  |
| --- |
| 1250mg after each HD |
| 1000mg after each HD |
| Continue current MD regimen |
| Continue current MD regimen |
| Decrease dose by 250mg |
| Hold Vancomycin  |

 |
| >110kg | 2500 mg  | 1000mg after HD | 1250mg after HD |

|  |
| --- |
| Cp < 10 mcg/mL |
| Cp 10-14.9 mcg/mL |
| Cp 15-19.9 mcg/mL |
| Cp 20-24.9 mcg/mL |
| Cp 25-30 mcg/mL |
| Cp >30 mcg/mL |

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|  |
| --- |
| 1250mg after each HD |
| 1250mg after each HD |
| Continue current MD regimen |
| Continue current MD regimen |
| Decrease dose by 250mg |
| Hold Vancomycin  |

 |

*^ if loading dose given on a non-HD day, check a random level with morning labs on the subsequent day of HD and administer a supplemental 500 mg dose post-HD if level <24.9; then proceed with above maintenance dosing on next regularly scheduled HD day.*

*Peritoneal dialysis (PD)*

* 15-20 mg/kg IV once to twice per week is usually adequate.
* Serum concentrations should be checked with am labs 24-48 hours after the first dose to ensure patient was adequately loaded, and patients should be re-dosed when Cmin <15-20 mcg/mL.

*Continuous Renal Replacement Therapy (CRRT*)

* + - Loading dose: 20-25 mg/kg
		- Vancomycin dose is based on the effluent flow rate or estimated CrCL. It is recommended to dose based on random levels until patient is on a stable CRRT rate. CRRT factors that may warrant evaluation of a random concentration due to changes in drug removal:
			* Abrupt CRRT initiation, interruption, or discontinuation
			* Changes in ultrafiltration rate
			* Alterations in residual patient renal function
		- Consider TDM at 12 or 24 hours to assess clearance and target attainment.

|  |  |  |
| --- | --- | --- |
| Effluent Flow Rate | Estimated CrCL | Dose Recommendations |
| <1500 mL/hr | <30 | 7.5-10 mg/kg IV q24h OR dose by random level |
| 1500-3000 mL/hr | 30-50 | 10-15 mg/kg IV q24h |
| >3000 mL/hr | >50 | 7.5-10 mg/kg IV q12h |

*Dosing by random levels (e.g., for acute kidney injury)*

* Vancomycin clearance is dramatically decreased and unpredictable in patients with AKI. Population-based PK equations used in calculators will not accurately predict the elimination rate (Ke).
* Dosing based on random levels should be considered with hemodynamic instability, shock, decreased urine output, significant changes in CrCL/SCr, and/or new or increasing vasopressor dosing requirements.
* A random level will be required after 1-2 doses (including LD). This level, along with daily SCr changes, will provide guidance to subsequent maintenance dosing. Levels should be ordered based on estimated half-life.
* Once SCr and CrCl have stabilized (e.g. no more than 20% variability day to day in SCr), then a final maintenance regimen can be recalculated.

# References:

1. Lodise T, et al. Vancomycin exposure in patients with methicillin-resistant Staphylococcus aureus bloodstream infections: how much is enough? Clin Infect Dis. 2014 Sep 1;59(5):666-75.
2. Neely M, et al. Are vancomycin trough concentrations adequate for optimal dosing? Antimicrob Agents Chemother. 2014;58(1):309-16.
3. Bosso J, et al. Relationship between Vancomycin Trough Concentrations and Nephrotoxicity: a Prospective Multicenter Trial. [Antimicrob Agents Chemother](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3232787/). 2011 Dec; 55(12): 5475–5479.
4. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother. 2013; 57(2):734-744.
5. Aljefri DM, Avedissian SN, Rhodes NJ, Postelnick MJ, Nguyen K, Scheetz MH. Vancomycin area under the curve and acute kidney injury: a meta-analysis. Clin Infect Dis. 2019; 69(11):1881-1887.
6. Suzuki Y, Kawasaki K, Sato Y et al. Is peak concentration needed in therapeutic drug monitoring of vancomycin? A pharmacokinetic-pharmacodynamic analysis in patients with methicillin resistant Staphylococcus aureus pneumonia. Chemotherapy. 2012; 58(4):308-312.
7. Hao JJ, Chen H, Zhou JX. Continuous versus intermittent infusion of vancomycin in adult patients: a systematic review and meta-analysis. Int J Antimicrob Agents 2016;47:28–35.
8. Shakeraneh P, Fazili T, Wang D, et al. Nephrotoxicity Risk and Clinical Effectiveness of Continuous versus Intermittent Infusion Vancomycin Among Patients in an Outpatient Parenteral Antimicrobial Therapy Program. Pharmacotherapy. 2020;40(4):357-362.
9. Ma NH, Walker SAN, Elligsen M, et al. Retrospective multicentre matched cohort study comparing safety and efficacy outcomes of intermittent-infusion versus continuous-infusion vancomycin. J Antimicrob Chemother. 2020;75(4):1038-1046.
10. Rybak MJ, 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(11):835-64.
11. Jumah MTB, Vasoo S, Menon S, et al. Pharmacokinetic/Pharmacodynamic Determinants of Vancomycin Efficacy in Enterococcal Bacteremia. Antimicrob Agent Chemother 2017;62:e01602-17.

# Appendices

1. Pharmacokinetic Equations for Therapeutic Drug Monitoring of Vancomycin

Population Pharmacokinetic Estimates

|  |  |  |
| --- | --- | --- |
| **Step** | **Equation** | **Notes** |
| 1. Estimate creatinine clearance (CrCL, mL/min)
 | $$CrCL= \frac{\left(140-age\right)\*BW}{72\*SCr} \left[ \*0.85 if female\right]$$ | BW=Body weight |
| 1. Estimate clearance (CL, L/h)
 | $$CL=0.75\*CrCL\*0.06$$ |  |
| 1. Estimate volume of distribution (Vd, L)
 | $$Vd=0.7 L/kg$$ |  |
| 1. Estimate rate of elimination (Ke, h-1)
 | $$Ke=0.00083\*CrCL+ 0.0044$$OR$$Ke= \frac{CL}{Vd}$$ |  |
| 1. Estimate half-life (T1/2, h)
 | $$T1/2=\frac{0.693}{Ke}$$ |  |
| 1. Estimate Dose24 using target AUC24 (mg)
 | $Dose24=CL\*AUC$24 |  |
| 1. Estimate Tau (h)
 | $$Tau= \frac{ln⁡(\frac{Cmax}{Ctr})}{Ke}+tinf$$ | tinf=Time of infusion |
| 1. Estimate new MD (mg)
 | $$MD= \frac{Dose24}{{24}/{Tau}}$$ |  |
| 1. Estimate new C­max (mg/L)
 | $$Cmax= \frac{{MD}/{tinf}}{Ke\*Vd}\*\left(\frac{1-e^{-Ke\*tinf}}{1-e^{-Ke\*tau}}\right)$$ |  |
| 1. Estimate new Ctr (mg/L)
 | $$Ctr=Cmax\* e^{-Ke\left(Tau-tinf\right)}$$ |  |
| 1. Estimate new AUC24 (mg\*h/L)
 | $$AUC24=({Dose}/{(Ke\*Vd))\*(24/tau)}$$OR$$AUCinf= \frac{(Cmax+Cmin)}{2}\*tinf$$$$AUCelim= \frac{(Cmax-Cmin)}{Ke}$$$$AUC24=\left(AUCinf+AUCelim\right)\*(\frac{24}{Tau})$$ |  |

Two-Level Pharmacokinetic Calculations for Patients at Steady-State (Non-Trapezoidal Method)

|  |  |  |
| --- | --- | --- |
| **Step** | **Equation** | **Notes** |
| 1. Calculate rate of elimination (Ke, h-1)
 | $$Ke= \frac{{ln(C1}/{C2)}}{∆T}$$ | C1=Higher concentrationC2=Lower concentration∆T=Time between concentrations |
| 1. Calculate half-life (T1/2, h)
 | $$T1/2=\frac{0.693}{Ke}$$ |  |
| 1. Calculate peak (Cmax, mg/L)
 | $$Cmax={C1}/{e^{-Ket'}}$$OR$$Cmax=C1\*e^{Ke\*t'}$$ | t’=Time between C1 and end of infusion (h) |
| 1. Calculate trough (Ctr, mg/L)
 | $$Ctr=C2\*e^{-Ket^{'}}$$OR$$Ctr=Cmax\*e^{-Ke(Tau-tinf)}$$ | t’=Time between C2 and true Ctr (h)Tau=Dosing intervaltinf=Time of infusion |
| 1. Calculate volume of distribution (Vd, L)
 | $$Vd= \frac{\frac{MD}{t}(1-e^{-Ke\*tinf})}{Ke\*Cmax\*(1-e^{-Ke\*tau})}$$OR$$Vd= \frac{\frac{MD}{t}(1-e^{-Ke\*tinf})}{Ke\*(Cmax-[Ctr\*e^{-Ke\*tinf}])}$$ | MD = Maintenance dosetinf=Time of infusion |
| 1. Calculate clearance (CL, L/h)
 | $$CL=Vd\*Ke$$ |  |
| 1. Calculate AUC24 (mg\*h/L)
 | $$AUC24=({Dose}/{(Ke\*Vd))\*(24/Tau)}$$ |  |
| 1. Calculate new Dose24 to achieve target AUC24(mg)
 | $$Dose24=CL\*AUC24$$ |  |
| 1. Calculate the new Tau (h)
 | $$Tau= \frac{{ln(Cmax,desired}/{Ctr,desired)}}{Ke}+tinf$$ |  |
| 1. Calculate new MD (mg)
 | $$MD=\frac{Dose24}{{24}/{Tau}}$$ |  |

Two-Level Pharmacokinetic Calculations for Patients at Steady-State (Trapezoidal Method)

|  |  |  |
| --- | --- | --- |
| **Step** | **Equation** | **Notes** |
| 1. Calculate rate of elimination (Ke, h-1)
 | $$Ke= \frac{{ln(C1}/{C2)}}{∆T}$$ | C1=Higher concentrationC2=Lower concentration∆T=Time between concentrations |
| 1. Calculate half-life (T1/2, h)
 | $$T1/2=\frac{0.693}{Ke}$$ |  |
| 1. Calculate peak (Cmax, mg/L)
 | $$Cmax={C1}/{e^{-Ket'}}$$OR$$Cmax=C1\*e^{Ke\*t'}$$ | t’=Time between C1 and end of infusion (h) |
| 1. Calculate trough (Ctr, mg/L)
 | $$Ctr=C2\*e^{-Ket^{'}}$$OR$$Ctr=Cmax\*e^{-Ke(Tau-tinf)}$$ | t’=Time between C2 and true Ctr (h)Tau=Dosing intervaltinf=Time of infusion |
| 1. Calculate volume of distribution (Vd, L)
 | $$Vd= \frac{\frac{MD}{t}(1-e^{-Ke\*tinf})}{Ke\*Cmax\*(1-e^{-Ke\*Tau})}$$OR$$Vd= \frac{\frac{MD}{t}(1-e^{-Ke\*tinf})}{Ke\*(Cmax-[Ctr\*e^{-Ke\*tinf}])}$$ | MD = Maintenance dosetinf=Time of infusion |
| 1. Calculate clearance (CL, L/h)
 | $$CL=Vd\*Ke$$ |  |
| 1. Calculate AUC24 (mg\*h/L)
 | $$AUCinf= \frac{(Cmax+Cmin)}{2}\*tinf$$$$AUCelim= \frac{(Cmax-Cmin)}{Ke}$$$$AUC24=\left(AUCinf+AUCelim\right)\*(\frac{24}{Tau})$$ |  |
| 1. Calculate new Dose24 to achieve target AUC24(mg)
 | $$Dose24=CL\*AUC24$$ |  |
| 1. Calculate the new Tau (h)
 | $$Tau= \frac{{ln(Cmax,desired}/{Ctr,desired)}}{Ke}+tinf$$ |  |
| 1. Calculate new MD (mg)
 | $$MD=\frac{Dose24}{{24}/{Tau}}$$ |  |

Two-Level Pharmacokinetic Calculations for Patients within the First 24 Hours of Therapy

|  |  |  |
| --- | --- | --- |
| **Step** | **Equation** | **Notes** |
| 1. Calculate rate of elimination (Ke, h-1)
 | $$Ke= \frac{{ln(C1}/{C2)}}{∆T}$$ | C1=Higher concentrationC2=Lower concentration∆T=Time between concentrations |
| 1. Calculate half-life (T1/2, h)
 | $$T1/2=\frac{0.693}{Ke}$$ |  |
| 1. Calculate peak (Cmax, mg/L)
 | $$Cmax={C1}/{e^{-Ket'}}$$OR$$Cmax=C1\*e^{Ke\*t'}$$ | t’=Time between C1 and end of infusion (h) |
| 1. Calculate volume of distribution (Vd, L)
 | $$Vd= \frac{\frac{Dose}{t}(1-e^{-Ke\*tinf})}{Ke\*Cmax}$$ | tinf=Time of infusion |
| 1. Calculate clearance (CL, L/h)
 | $$CL=Vd\*Ke$$ |  |
| 1. Calculate the Dose24 required to achieve target AUC24 (mg)
 | $$Dose24= CL\*AUC24$$ |  |
| 1. Calculate the new Tau (h)
 | $$Tau= \frac{{ln(Cmax,desired}/{Ctr,desired)}}{Ke}+tinf$$ |  |
| 1. Calculate new MD (mg)
 | $$MD=\frac{Dose24}{{24}/{Tau}}$$ | MD=Maintenance dose |
| 1. Estimate new AUC24 (mg\*h/L)
 | $$AUC24=({MD}/{(Ke\*Vd))\*(24/Tau)}$$OR$$AUCinf= \frac{(Cmax+Cmin)}{2}\*tinf$$$$AUCelim= \frac{(Cmax-Cmin)}{Ke}$$$$AUC24=\left(AUCinf+AUCelim\right)\*(\frac{24}{Tau})$$ |  |