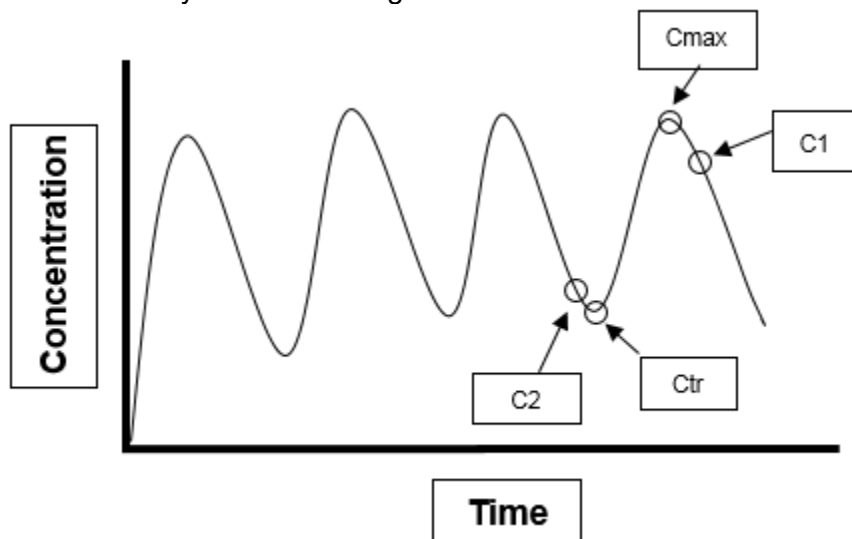


VANCOMYCIN DOSING AND MONITORING IN ADULTS

Evidence for AUC₂₄-based Dosing and Monitoring:

- An AUC₂₄/MIC of 400 was found to be the pharmacodynamic parameter best correlated with vancomycin activity against *Staphylococcus aureus* (*S. aureus*).¹
- Poor correlation of serum troughs with true AUC₂₄: Troughs of 15-20 mg/L were previously used as surrogates for AUC₂₄ > 400 mg*h/L; however, this correlation was observed only 70-75% of the time. The 2-concentration AUC₂₄ method has been found to accurately correlate with a patient's true AUC₂₄ 97-98% of the time.^{2,3}
- Increased safety: Trough concentrations of 15-20 mg/L have been correlated with nephrotoxicity, while AUC₂₄ < 600 mg*h/L were associated with decreased vancomycin-associated acute kidney injury (AKI), likely due to decreased total daily doses.^{4,5,6,7}
- Similar or increased efficacy: Evidence suggests an AUC₂₄ > 400 has been shown to decrease treatment failure, defined as 30-day all-cause mortality, persistent bacteremia, or recurrence.^{8,9,10}
- Rationale for targeting AUC₂₄ rather than AUC₂₄/MIC
 - Studies evaluating AUC₂₄/MIC used broth microdilution to determine the MIC of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates to vancomycin. UKHC does not routinely utilize this method of susceptibility testing.
 - The majority of isolates tested by UKHC's automated testing have MICs of 1 mg/L so the AUC₂₄/MIC would be equivalent to the AUC₂₄.
 - If the MRSA MIC to vancomycin is 2 mg/L, this could be due to expected variability with susceptibility testing (i.e., an MIC of 1 mg/L could be 0.5 mg/L or 2 mg/L). In these scenarios, clinical evaluation of the patient is essential to determine if vancomycin should be continued or replaced with an alternative. Call the antimicrobial stewardship team if there are questions regarding management.
- The studies supporting AUC₂₄ were done primarily in patients with *S. aureus* infections and are being extrapolated to management of other pathogens. This is similar to what was historically done with troughs.



Time of Sampling and Recommended Frequency:

Patients in whom vancomycin serum drug concentrations should NOT be obtained:

- Adult patients <60 yo with normal body weight, stable renal function with $Cl_{cr} > 40$ ml/min, and short course therapy (e.g., < 3 days)

First-dose pharmacokinetics:

- Consider obtaining two serum concentrations (C1 and C2) after the first dose in patients with the following:¹¹
 - Suspected or proven MRSA bacteremia
 - Sepsis (if MRSA coverage is warranted)
 - Severe infections (pneumonia, infective endocarditis, osteomyelitis, meningitis)
 - Consider in patients at high risk for nephrotoxicity including renal transplant, obesity, receipt of concomitant nephrotoxic agents, etc.

While C1 and C2 concentration results are pending, use clinical judgment to determine if a one-time empiric maintenance dose should be ordered. This may be beneficial when passing off patient care to another pharmacist or when a patient is admitted to a team without 24 hour pharmacist coverage. Additionally, this method can help to avoid a missed dose which can result in a delay in therapy. When the concentrations have resulted, determine patient-specific parameters as soon as possible to calculate a maintenance dose.

- When to obtain levels
 - Peak (C1) 2 hours after infusion is complete to allow for distribution
 - Random (C2) should be drawn **at least 1 half-life apart** from the peak at a time point based on the estimated Cl_{cr} , k , and $t_{1/2}$ using the table below

Creatinine Clearance (mL/min)	Elimination Rate, k (h^{-1}) ^α	$t_{1/2}$ (Hours)	Timing of Levels (Hours after Completion of Infusion)	
			Peak (C1)	Random (C2)
≥ 120	0.104	6.7	2	10
100	0.0874	7.9	2	10
80	0.0708	9.8	2	14
60	0.0542	12.8	2	16
40	0.0376	18.4	2	22
≤ 30	REFER TO RENALLY ADJUSTED DOSING METHODS			

^α Utilizes the modified Matzke equation: $k = (0.00083 * CrCl) + 0.0044$

Steady-state pharmacokinetic candidates:

- Patients NOT fitting into the first two categories above should have a peak (C1) and a trough (C2) obtained around the 4th dose after initiating therapy.
- When to obtain levels:
 - Troughs should be ordered within 30 minutes prior to the dose. Peaks should be ordered 2 hours after complete infusion of the dose to allow for distribution
 - Once at steady state, clinical judgment should be used to determine when to obtain levels; however, concentrations should be monitored no less frequently than 1 time/week. Specific populations may warrant more frequent monitoring.
 - For outpatient therapy, a trough concentration is likely all that will be obtained due to feasibility. This level should be correlated with the patient's most recent inpatient trough that was associated with an adequate AUC_{24} . Continuous infusion vancomycin can also be considered to allow for AUC_{24} monitoring.

Therapeutic Range-AUC₂₄ Goal:

- **AUC₂₄ goal of 500** is recommended with a range of 400-600
 - 500 is recommended instead of 400 due to decreased treatment failure rates with AUC₂₄ of 500 and due to patient variability^{1,12}
 - All patients should have two concentrations obtained with every evaluation to calculate the AUC₂₄ except for patients with developing or resolving acute kidney injury (AKI) where SCr is not stable and patients on dialysis. In these patients, troughs should be maintained between 15-20 mg/L to maintain an AUC₂₄ 400-600. Once renal function stabilizes in patients with AKI, 2 levels can be drawn similarly to patients without AKI. New renal transplant recipients, new start ECMO patients, or those immediately post-surgery may require trough monitoring until renal function stabilizes.

- **Role of troughs**
 - In patients with normal renal function or on CRRT, the primary goal is reaching the AUC target while maintaining a minimal trough to prevent AKI (AKI risk increases when > 15mg/L)¹⁶
 - When treating patients with a concern for meningitis, continue to dose and monitor patients with a goal AUC₂₄ of 500. Consider maintaining the trough between 15-20 mg/L in patients with meningitis due to limited data with intermittent dosing and AUC₂₄ monitoring. Continuous infusion can also be considered in these patients (see below).
 - In patients with unstable renal function, trough monitoring should be utilized due to fluctuating pharmacokinetics making AUC₂₄ monitoring impractical

Monitoring of Patients on Vancomycin ¹⁶			
Population	AUC ₂₄	Troughs	# of Levels
Cl _{cr} > 30 ml/min	500 (400-600 acceptable)	(15-20 mg/L for meningitis)	2
AKI or hemodialysis		15-20 mg/L	1 (troughs of 15-20 mg/L needed to achieve AUC ₂₄ goal)

Initial Loading Dose

- To achieve rapid attainment of the target concentration, a loading dose should be considered without regard to renal function. Loading doses are highly recommended for:
 - Sepsis or severe infection (bacteremia, pneumonia, infective endocarditis, osteomyelitis, meningitis)
 - Suspicion of volume overload
 - Initiation of continuous infusion vancomycin
 - Obesity
 - Requiring dialysis or renal replacement therapy
- Recommend a loading dose of 25-30 mg/kg based on ABW.¹⁵
 - 40-60kg = 1000 – 1500mg IV x 1
 - 61-80kg = 1500 – 2500mg IV X 1
 - 81-100kg = 2000– 3000 mg IV X 1
 - >100kg = consider maximum initial dose of 3000mg. More intensive and early therapeutic monitoring should be performed in obese patients

Dosing in Obesity

- Defined as a body mass index (BMI) ≥ 30 kg/m². Vd increases with actual body weight but is not reliably predictable in obese patients.
- Loading doses should be utilized with doses of 20-25 mg/kg with a maximum of 3000mg
- First dose pharmacokinetics are highly recommended in order to optimize dosing.
- Empiric maintenance doses for most should typically not exceed 4500mg/day
- Early and frequent monitoring of AUC should be done to decrease nephrotoxicity

Maintenance Dose Calculations for Intermittent Infusion

(empiric maintenance dosing in obese patients typically does not exceed 4500 mg/day)

Patients with First-Dose Kinetics

Use two levels obtained from the first dose to calculate a patient-specific maintenance dose.

1. Calculate patient-specific elimination rate (k).

$$k = \frac{\ln(C1_{random}/C2_{random})}{T'} \quad T' = \text{Time between C1 and C2}$$

2. Calculate patient-specific half-life ($t_{1/2}$)

$$t_{1/2} = \frac{0.693}{k}$$

3. Calculate C_{max}

$$C_{max} = C1/e^{-kt'} \quad t' = \text{time between C1 and end of the infusion}$$

4. Calculate volume of distribution (Vd)

$$Vd = \frac{LD(1-e^{-kt})}{k(C_{max})} \quad \begin{array}{l} LD = \text{loading dose (mg)} \\ t = \text{Infusion time} \end{array}$$

5. If $C2_{random}$ is high, calculate time to reach desired range to know when to restart vancomycin

$$t' = \frac{\ln(C_{tr,true}/C_{tr,desired})}{k}$$

6. Calculate clearance (Cl)

$$Cl = k \times Vd$$

7. Calculate total daily dose (TDD) of maintenance regimen

$$TDD = Cl \times AUC_{goal} \quad AUC_{24} \text{ goal} = 500 \text{ (Range of 400-600 acceptable)}$$

8. Use the following equations to determine the dosing interval (τ)

$$\tau = \frac{\ln(C_{max,desired}/C_{tr,desired})}{k} + t$$

$C_{max,desired}$: 40 μ g/mL
 $C_{tr,desired}$: 10 μ g/mL (want most efficacious but least nephrotoxic regimen that will still prevent resistance development)
t = infusion time

9. Calculate the new maintenance dose (MD)

$$MD = TDD / (24 / \tau) \quad * \text{Check the } AUC_{24} \text{ of your rounded MD: } AUC = \frac{AUC_{goal}}{TDD_{calculated}} * TDD_{actual (rounded)}$$

10. Calculate the expected C_{max} and C_{tr} of the new MD

$$C_{max,predicted} \text{ Adults: } = \frac{MD/Vd}{1-e^{-k\tau}} \quad \text{Pediatrics: } = \frac{MD * (1-e^{-kt})}{k * Vd * t (1-e^{-k\tau})} \quad \tau = \text{dosing interval}$$

$$C_{tr,predicted} = C_{pk,predicted} * e^{-k(\tau-t)} \quad t = \text{Infusion time}$$

C_{tr} goal 10-20 mg/L

Patients WITHOUT First-Dose Kinetics

Use population parameters to determine the maintenance dose that will follow the loading dose (if given). Once at steady state, obtain two levels for calculation of patient-specific parameters.

1. Calculate Cl_{cr} using Cockcroft-Gault or Salazar-Corcoran equation (if >125% X IBW)

2. Estimate Vd based on ABW

Normal Vd range: 0.5 – 0.9 L/kg (use average 0.7L/kg)

3. Estimate k using Cl_{cr}

$$k = 0.00083 (Cl_{cr}) + 0.0044$$

4. Estimate half-life ($t_{1/2}$)

$$t_{1/2} = \frac{0.693}{k}$$

5. Calculate clearance (Cl)

$$Cl = k * Vd$$

Consider the following Cl_v equation in obese patients: $9.656 - 0.078 * AGE - 2.009 * SCR + 1.09 * SEX + 0.04 * TBW^{0.75}$, where AGE is in years, SCR is in mg/dL, SEX is 1 if male and 0 if female and TBW is total body weight in kg

6. Calculate total daily dose (TDD) of maintenance regimen

$$TDD = Cl * AUC_{goal}$$

AUC_{24} goal = 500 (Range of 400-600 acceptable)

7. Estimate dosing interval (tau, τ)

$$\tau = \frac{\ln(C_{max,desired} / C_{tr,desired})}{k} + t$$

$C_{max,desired}$: 40 μ g/mL

$C_{tr,desired}$: 10 μ g/mL (want most efficacious but least nephrotoxic regimen that will still prevent resistance development)

t = infusion time

8. Calculate the Maintenance Dose (MD)

$$MD = TDD / (24 / \tau)$$

τ = dosing interval

9. Calculate the predicted C_{max} and C_{tr} based on MD and τ selected

$$C_{max,predicted} \text{ Adults: } = \frac{MD/Vd}{1-e^{-k\tau}} \quad \text{Pediatrics: } = \frac{MD*(1-e^{-kt})}{k*Vd*t(1-e^{-k\tau})}$$

τ = dosing interval
 t = Infusion time
 C_{tr} goal 10-20 mg/L

$$C_{tr,predicted} = C_{pk,predicted} \times e^{-k(\tau-t)}$$

10. If want to double check the AUC₂₄ that is likely after rounding the dose, use the following equation:

$$AUC = \frac{AUC_{goal}}{TDD_{calculated}} * TDD_{actual (rounded)} \quad AUC_{24} \text{ goal} = 500 \text{ (Range of 400-600 acceptable)}$$

Evaluation of AUC₂₄ at Steady State to Determine Dose Adjustments for Intermittent Infusion

The peak (C1) and trough (C2) obtained around the 4th dose should be utilized to calculate patient specific parameters to determine if dose adjustments need to be made.

1. Calculate patient-specific elimination rate (k).

$$k = \frac{\ln(C1/C2)}{T'}$$

T' is determined by subtracting the time difference between C1 and C2 from the Tau. For example, if the time difference between C1 and C2 was 1.5hrs and the Tau = q8hrs, then T' = (8 - 1.5) = 6.5hrs. *If both concentrations are drawn after the dose is given then can simply subtract the time difference between the two concentrations*

2. Calculate patient-specific half-life (t_{1/2})

$$t_{1/2} = \frac{0.693}{k}$$

3. Calculate the C_{max} and C_{tr} from C1 and C2, respectively

$$C_{max} = \frac{C1}{e^{-kt'}}$$

t' = Time between C1 as drawn and end of infusion

$$C_{tr} = C2 \times e^{-kt'}$$

t' = Time between C2 as drawn and C_{tr}

4. Calculate volume of distribution (Vd):

$$Vd = \frac{\frac{MD}{t}(1-e^{-kt})}{k(C_{max})(1-e^{-k\tau})}$$

MD = maintenance dose (mg)
 τ = dosing interval
 t = Infusion time

5. If measured C_{tr} is high, calculate time required to reach desired range to know when to restart vancomycin

$$t' = \frac{\ln(C_{tr,true}/C_{tr,desired})}{k}$$

6. Assess AUC₂₄ for goal of 500 and acceptable range of 400-600

TDD = total daily dose

$$AUC = \frac{TDD}{k * Vd}$$

7. If within goal, continue dosing. If NOT AT GOAL:

- Increase or decrease TDD proportionally to attain goal AUC₂₄.

$$TDD_{new} = \frac{TDD_{current}}{AUC_{current}} * AUC_{goal} \quad AUC_{24} \text{ goal} = 500 \text{ (Range of 400-600 acceptable)}$$

Once a maintenance dose is selected, can double check what your actual AUC₂₄ will be using proportions

- **Can also** use the following equations if want to determine dosing interval and anticipated peak and trough. Try to choose the regimen that provides an adequate AUC₂₄ but has a lower estimated trough to limit the risk of nephrotoxicity

Calculate tau:

$$\tau = \frac{\ln(C_{max,desired}/C_{tr,desired})}{k} + t$$

$C_{max,desired}$: 40 µg/mL
 $C_{tr,desired}$: 10 µg/mL
 t = infusion time

Calculate predicted C_{max} and C_{tr}:

$$C_{max,predicted} \text{ Adults: } = \frac{MD/Vd}{1-e^{-k\tau}} \quad \text{Pediatrics: } = \frac{MD*(1-e^{-kt})}{k*Vd*t(1-e^{-k\tau})}$$

τ =dosing interval
 t = Infusion time
 C_{tr} goal 10-20 mg/L

$$C_{tr,predicted} = C_{pk,predicted} * e^{-k(\tau-t)}$$

8. Follow-up concentrations –should be monitored no less frequently than 1 time per week once at steady state. Two concentrations should still be obtained around the dose to calculate the AUC₂₄. As an outpatient, a trough is likely all that will be obtained due to feasibility.

General Guidelines for Continuous Infusion Dosing and Monitoring

Possible Indications for Initiation of Continuous Infusion:

- Unable to obtain therapeutic AUC₂₄ on intermittent dosing
- Increased total daily dose (>4000 mg per day)
- Critically ill patients

Practical Considerations

- Stable renal function or on CRRT (not on intermittent dosing)
- Ensure patient has sufficient access to allow for continuous infusion
- Assess for any compatibility issues
- Central line typically recommended but studies have used peripheral (<6mg/ml concentrations)
- Ensure levels are drawn away from the infusion site
- All continuous infusions are pre-built in 500ml. Please do not alter pre-built orders.

Initiating a Continuous Infusion from Initiation of Therapy

- Must use a loading dose of 25-30 mg/kg

- Maintenance dosing can be based on an empiric dose of 30 mg/kg/day to start after completion of loading dose or based on first-dose PK
 - First-dose PK used:
 - if C₂ (second random level) is < 17 µg/mL, consider a mini-loading dose:
 - Mini-load Dose = (25-C₂) x V_d to achieve AUC₂₄ coverage while continuous infusion reaches steady state.
 - Use calculations from “Maintenance Dose Calculation in Patients with First-Dose Kinetics” to calculate the total daily dose (TDD) for the maintenance regimen. Begin continuous infusion after C₂ has resulted and maintenance regimen calculated.
 - *Maintenance Dose (mg/hr) = TDD/(24 hours)*

Converting from Intermittent to Continuous Infusion

- Use the new desired TDD and calculate using maintenance dose equation above

Monitoring AUC₂₄ at Steady State

- A single random level should be collected at steady state (level should be drawn from a different line than vancomycin is infusing in).
 - Steady state depends on estimated half-life, which can be determined by using population-based kinetics k equation detailed above, but obtaining one around 36-48 hours is reasonable.
- Calculate AUC₂₄ from a single level at steady state. A goal AUC₂₄ of 400-600 corresponds to random levels between 17-25 mg/L.

$$AUC_{24} = \text{Vancomycin level at steady state} \times 24$$
- If random level at steady state < 17 mg/L, give mini-loading dose using equation described above.
- To adjust continuous infusion rate, see process above for intermittent dosing to adjust the TDD to target AUC₂₄.

GUIDELINES FOR DOSING IN RENAL IMPAIRMENT

Conventional Intermittent Hemodialysis (IHD)

Dose

1. Loading dose of 25-35 mg/kg based on ABW (consider maximum of 3000mg)
2. Enter “intermittent” vancomycin order as an active order between doses

Timing and Dialyzer Permeability	Vancomycin Loading Dose, mg/kg	Vancomycin Maintenance Dose, mg/kg
After dialysis ends		
Low permeability	25	7.5 ^b
High permeability	25	10 ^b
Intradialytic		
Low permeability	30	7.5-10 ^b
High permeability	35	10-15 ^b

^bThrice-weekly dose administration

Effect of hemodialysis at UKHC

3. Vancomycin clearance is affected by “high-flux” hemodialysis with removal of 30-40% during a full hemodialysis session (e.g., 3-5 hours)
4. Elimination may also be affected by the residual kidney function of the patient. The effect of extrarenal mechanisms of elimination are limited in end-stage renal disease (ESRD).
5. Average half-life in ESRD patients is 6-9 days depending on residual kidney function and high-flux dialysis clearance (7.5 days in an anephric patient).
6. Maintaining predialysis concentrations between 15-20 mg/L is likely to achieve AUC of 400-600 mg*h/L in the previous 24 hours

Concentrations

1. Usually drawn 3-5 days post-dose ordered as a random level, but may be drawn sooner
2. Redose when pre-dialysis level is expected to be ≤ 15 mg/L (< 20mg/L for life threatening infections, see above in “Therapeutic ranges”).
3. Levels drawn up to 12 hours following high-flux hemodialysis may be misleading due to redistribution. Obtaining a level prior to hemodialysis is preferred.

Continuous Renal Replacement Therapy (CRRT)

- Consider loading dose of 20-25 mg/kg by ABW (consider maximum of 3000mg)
- Utilize the same dosing strategies as those outlined above for patients with stable renal function. Keep in mind that it can take 1-2 days for the patient’s VD to stabilize
- Factors that may lead to changes in amount of drug removed
 - Changes in ultrafiltration rate
 - Dialysis interrupted (i.e. filter clotted, particularly overnight)
 - Alterations in existing renal function (ARF vs CRF)

Acute Kidney Injury or Unstable Renal Function

- Monitor troughs and re-dose when concentration <20 mg/L
- Troughs of 15-20 mg/L typically needed to achieve AUC₂₄ goal.
- Two levels should be checked once renal function stabilizes to individualize dosing.

GUIDELINES FOR VANCOMYCIN DOSING IN PEDIATRICS

Neonatal Empiric Vancomycin Dosing (Assuming normal renal function)		
Postmenstrual Age*	Postnatal Age#	Dose
≤ 28 wks	≤ 2 wks old	15 mg/kg q18hr
≤ 28 wks	> 2 wks old	15 mg/kg q12hr
29-43.6 wks	≤ 2 wks old	15 mg/kg q12hr
29-43.6 wks	> 2 wks old	15 mg/kg q8hr
≥44 wks	15 mg/kg q6hr	
Pediatric Empiric Vancomycin Dosing (PMA ≥ 44 weeks; Assuming normal renal function)^{1,2,3,4}		
Based on Indication and Age	<i>Bacteremia, SSTI, Pneumonia, Bone/Joint Infections, CF Exacerbation</i>	<i>Meningitis, Complicated Pneumonia</i>
1 mo – 8 yrs	70 mg/kg/day divided q6hr	80 mg/kg/day divided q6hr
9 – 12 yrs	60 mg/kg/day divided q6hr	70 mg/kg/day divided q6hr
13 – 16 yrs	60 mg/kg/day divided q8hr	70 mg/kg/day divided q6hr
> 16 yrs	15 – 20 mg/kg q8-12hr (similar to adult dose)	
<i>IDSA guidelines recommend a maximum empiric daily dose of 3,600 mg of vancomycin in pediatrics. For patients weighing >40-50 kg, consider utilizing first-dose pharmacokinetics as early monitoring of measured concentrations is recommended in patients receiving >3,000 mg/day of vancomycin.¹</i>		
Dosing Pearls		
Renal Impairment**	<ul style="list-style-type: none"> • Neonates <ul style="list-style-type: none"> ○ Urine output <0.5 mL/kg/hr or concern for rapid decline in renal function: administer a one-time dose of IV vancomycin and obtain level 18-24 hours following dose to assess clearance. ○ Age <1 year has been independently associated with late-onset vancomycin-associated acute kidney injury (AKI).⁸ • Pediatric patients <ul style="list-style-type: none"> ○ GFR <90 mL/min: extend dosing interval (i.e. q6hr to q8hr) and consider first-dose kinetics. 	
Obesity	<ul style="list-style-type: none"> • BMI >95th percentile, use actual body weight^{4,6} • Consider loading dose of 20 mg/kg based on actual body weight 	
Congenital Heart Disease	<ul style="list-style-type: none"> • Pediatric patients post-cardiopulmonary bypass: empiric starting dose of 15 mg/kg/dose every 12 hours • Pediatric patients with history of heart failure: empiric starting dose of 15 mg/kg/dose every 8 to 12 hours 	
Oncology Patients	<ul style="list-style-type: none"> • Consideration of lower dosing in pediatric oncology patients should be given for patients who have received nephrotoxic chemotherapy in the preceding 24-72 hours 	
Administration	<ul style="list-style-type: none"> • Final intravenous concentration must be ≤5 mg/mL; may use 10mg/mL through central line if fluid restricted. • Infuse all doses over at least 1 hour. Doses >1g may be infused at a maximum rate of 1g/hour 	

*Postmenstrual Age = gestational age plus postnatal age in weeks (i.e., PMA= 34 weeks for 3-week-old neonate born at 31 weeks gestation); #Postnatal Age = age after birth; **The Bedside Schwartz equation may be used to estimate GFR in pediatrics.⁷ GFR may be overestimated in patients with decreased muscle mass.

Pediatric Vancomycin Monitoring Pearls	
AUC ₂₄ Monitoring	<p>Target AUC₂₄ is 400 mg*hr/L (up to maximum AUC₂₄ of 600 mg*hr/L)</p> <ul style="list-style-type: none"> Given the lack of evidence to support the higher end of the AUC₂₄ range in pediatrics, it is prudent to target an AUC₂₄ of 400 mg*hr/L to mitigate the risk of nephrotoxicity.¹
Level Attainment	<ul style="list-style-type: none"> If therapy to continue beyond 48 hours: check steady-state trough (5-15 minutes prior to dose) and peak (1 hour after the end of the infusion/flush) <ul style="list-style-type: none"> Trough should be drawn at least 1 half-life apart from the peak TDM should be performed at least once weekly or more frequently in patients with fluctuating renal function/fluid status, lack of clinical response, or persistently positive blood cultures.
Role of Troughs	<ul style="list-style-type: none"> In patients with normal renal function or on CRRT, the primary goal is to achieve AUC₂₄ of 400 mg*hr/L while minimizing trough concentrations to prevent nephrotoxicity. There is no evidence to support targeting a minimum trough concentration in pediatric patients monitored using AUC₂₄. Lower trough concentrations of 7-10 mg/L, rather than 15 to 20 mg/L (as in adults), correlate with AUC/MIC >400 mg*hr/L in pediatric patients.^{1,2} Trough concentrations ≥15 mg/L have been associated with a 2.5 to 2.7-fold increase in risk of AKI in pediatric patients.^{9,10} When treating patients with a concern for meningitis, continue to dose and monitor patients with a goal AUC₂₄ of 400 mg*hr/L. In patients with unstable renal function, trough monitoring should be utilized, in place of AUC₂₄ monitoring, due to fluctuating pharmacokinetics In patients with CF in whom AUC₂₄ calculations are not feasible, may consider trough monitoring with a target trough of 10-20 mg/L.
Patients with Renal Dysfunction <i>GFR <30 mL/min or receiving intermittent hemodialysis</i>	<ul style="list-style-type: none"> Enter "intermittent" vancomycin order Monitor random level and re-dose vancomycin when <u>measured</u> trough concentration is <15 mg/L for invasive infections or <10 mg/L for SSTI and non-MRSA bacteremia¹ <ul style="list-style-type: none"> <i>Goal trough¹ for SSTI, non-MRSA bacteremia: 10-15 mg/L</i> <i>Goal trough¹ for meningitis, MRSA bacteremia, osteomyelitis, pneumonia, endocarditis: 15-20 mg/L</i>
Monitoring	<ul style="list-style-type: none"> Renal function: UOP, BUN, and Scr must be monitored every 24 hours if vancomycin continued beyond 48 hours per NINJA criteria. <ul style="list-style-type: none"> BOTH serum concentrations and renal function must be closely monitored as vancomycin clearance and GFR are not always well correlated in pediatrics.¹ Clinical status: fever curve, culture results, markers of inflammation
Alternative Therapies	<ul style="list-style-type: none"> Most pediatric patients should not require more than 3,000 mg/day of vancomycin. The maximum empiric daily dose is 3,600 mg.¹ The safety of vancomycin at doses >80 mg/kg/day has not been prospectively evaluated and avoidance of vancomycin exceeding doses of 100 mg/kg/day is recommended.¹ Consultation with antimicrobial stewardship should be considered for any patient in which alternative therapies are being considered.

Maintenance Dose Calculations for Intermittent Infusion in Pediatrics

(Empiric maintenance dosing in pediatric patients typically should not exceed 3600 mg/day)

Patients with First-Dose Kinetics

Use two levels obtained from the first dose to calculate a patient-specific maintenance dose.

1. Calculate patient-specific elimination rate (k).

$$k = \frac{\ln(C1_{random}/C2_{random})}{T'} \quad T' = \text{Time between C1 and C2}$$

2. Calculate patient-specific half-life ($t_{1/2}$)

$$t_{1/2} = \frac{0.693}{k}$$

3. Calculate C_{max}

$$C_{max} = C1/e^{-kt'} \quad t' = \text{time between C1 and end of the infusion}$$

4. Calculate volume of distribution (Vd)

$$Vd = \frac{\frac{LD}{t}(1-e^{-kt})}{k(C_{max})} \quad \begin{array}{l} LD = \text{loading dose (mg)} \\ t = \text{Infusion time} \end{array}$$

5. If $C2_{random}$ is high, calculate time to reach desired range to know when to restart vancomycin

$$t' = \frac{\ln(C_{tr,true}/C_{tr,desired})}{k}$$

6. Calculate clearance (Cl)

$$Cl = k \times Vd$$

7. Calculate total daily dose (TDD) of maintenance regimen

$$TDD = Cl \times AUC_{goal} \quad AUC_{24} \text{ goal} = 400 \text{ (up to 600 acceptable)}$$

8. Use the following equations to determine the dosing interval (τ)

$$\tau = \frac{\ln(C_{max,desired}/C_{tr,desired})}{k} + t \quad \begin{array}{l} C_{max,desired}: 40 \mu\text{g/mL} \\ C_{tr,desired}: 5 \mu\text{g/mL (want least nephrotoxic regimen)} \\ t = \text{infusion time} \end{array}$$

9. Calculate the new maintenance dose (MD)

$$MD = TDD/(24/\tau) \quad \text{*Check the } AUC_{24} \text{ of your rounded MD: } AUC = \frac{AUC_{goal}}{TDD_{calculated}} * TDD_{actual (rounded)}$$

10. Calculate the expected C_{max} and C_{tr} of the new MD

$$\begin{array}{l} C_{max,predicted} = \frac{MD*(1-e^{-kt})}{k*Vd*t(1-e^{-k\tau})} \\ C_{tr,predicted} = C_{pk,predicted} \times e^{-k(\tau-t)} \end{array} \quad \begin{array}{l} \tau = \text{dosing interval} \\ t = \text{Infusion time} \end{array}$$

Evaluation of AUC₂₄ at Steady State to Determine Dose Adjustments for Intermittent Infusion in Pediatrics

The peak (C₁) and trough (C₂) obtained around the 4th dose should be utilized to calculate patient specific parameters to determine if dose adjustments need to be made.

1. Calculate patient-specific elimination rate (k).

$$k = \frac{\ln(C_1/C_2)}{T'}$$

T' is determined by subtracting the time difference between C₁ and C₂ from the Tau. For example, if the time difference between C₁ and C₂ was 1.5hrs and the Tau = q8hrs, then T' = (8 - 1.5) = 6.5hrs. *If both concentrations are drawn after the dose is given then can simply subtract the time difference between the two concentrations*

2. Calculate patient-specific half-life (t_{1/2})

$$t_{1/2} = \frac{0.693}{k}$$

3. Calculate the C_{max} and C_{tr} from C₁ and C₂, respectively

$$C_{max} = \frac{C_1}{e^{-kt'}}$$

t' = Time between C₁ as drawn and end of infusion

$$C_{tr} = C_2 \times e^{-kt'}$$

t' = Time between C₂ as drawn and C_{tr}

4. Calculate volume of distribution (Vd):

$$Vd = \frac{\frac{MD}{t}(1-e^{-kt})}{k(C_{max})(1-e^{-k\tau})}$$

MD = maintenance dose (mg)

τ = dosing interval

t = Infusion time

5. If measured C_{tr} is high, calculate time required to reach desired range to know when to restart vancomycin

$$t' = \frac{\ln(C_{tr,true}/C_{tr,desired})}{k}$$

6. Assess AUC₂₄ for goal of 500 and acceptable range of 400-600

$$AUC = \frac{TDD}{k * Vd}$$

TDD = total daily dose

7. If within goal, continue dosing. If NOT AT GOAL:

- Increase or decrease TDD proportionally to attain goal AUC₂₄.

$$TDD_{new} = \frac{TDD_{current}}{AUC_{current}} * AUC_{goal} \quad AUC_{24} \text{ goal} = 400 \text{ (up to 600 acceptable)}$$

Once a maintenance dose is selected, can double check what your actual AUC₂₄ will be using proportions

- **Can also** use the following equations if want to determine dosing interval and anticipated peak and trough. Try to choose the regimen that provides an adequate AUC₂₄ but has a lower estimated trough to limit the risk of nephrotoxicity

8. Calculate tau:

$$\tau = \frac{\ln(C_{max,desired}/C_{tr,desired})}{k} + t$$

$C_{max,desired}$: 40 µg/mL
 $C_{tr,desired}$: 5 µg/mL
t = infusion time

9. Calculate predicted C_{max} and C_{tr} :

$$C_{max,predicted} = \frac{MD*(1-e^{-kt})}{k*Vd*t(1-e^{-k\tau})}$$

τ =dosing interval
t = Infusion time

$$C_{tr,predicted} = C_{pk,predicted} \times e^{-k(\tau-t)}$$

10. Follow-up concentrations –should be monitored no less frequently than 1 time per week once at steady state. Two concentrations should still be obtained around the dose to calculate the AUC_{24} . As an outpatient, a trough is likely all that will be obtained due to feasibility.

Continuous Infusion Vancomycin in Pediatric Patients:¹¹⁻¹³

Possible Indications for Initiation of Continuous Infusion:

- Unable to obtain therapeutic AUC₀₋₂₄ on intermittent dosing

Initiating a Continuous Infusion from Initiation of Therapy

- Must use a loading dose of 25-30 mg/kg
- Initiate maintenance dose immediately following completion of the bolus dose
 - Pediatric patients often need less from a total daily dose, compared to traditional intermittent dosing.
 - Available evidence suggests doses 40 to 50 mg/kg/day, adjusted based on therapeutic drug monitoring
 - Pediatric patients with cystic fibrosis may require total daily doses of 60 to 70 mg/kg/day

Converting from Intermittent to Continuous Infusion

- Use the new desired TDD and calculate using maintenance dose equation

$$\text{Maintenance Dose (mg/hr)} = \text{TDD}/(24 \text{ hours})$$

Monitoring AUC₀₋₂₄ at Steady State

- Draw a single random level at steady state (level should be drawn from a different line than vancomycin is infusing in).
- Calculate AUC₀₋₂₄ from a single level at steady state. A goal AUC₀₋₂₄ of 400-600 corresponds to random levels between 17-25 mg/L.
$$\text{AUC}_{0-24} = \text{Vancomycin level at steady state} \times 24$$
- If random level at steady state < 17 mg/L, consider providing a mini-bolus
- To adjust continuous infusion rate, see process above for intermittent dosing to adjust the TDD to target AUC₀₋₂₄.

DOCUMENTATION AND PRACTICE PROBLEMS

WRITE A CHART NOTE. Document pertinent clinical monitoring parameters, dose recommendations and estimated and/or calculated pharmacokinetic parameters in the medical record using the "Pharmacy Vancomycin Monitoring" note. (Also refer to *Department of Pharmacy Guidelines for Writing Notes in Patient Charts, PH-02-04*)

- Briefly describe the rationale of the drug and determine if warranted based on clinical and patient information.
- Document the current day of therapy and goal length of therapy (e.g., Day #2/14 vancomycin), and any concomitant antibiotics.
- Document the collection times of the reported concentrations and note if the samples were obtained appropriately. For example, if C1 was drawn late or if C2 was drawn early.
- Include the calculated PK parameters: K (hr⁻¹), t_{1/2} (hrs), Vd (L) and Vd (L/kg). Also calculate AUC₂₄
- Write a new dosage in mg and mg/kg/dose (e.g., vancomycin 1000 mg IV q12hrs, 15mg/kg/dose).
- When changing a dosage, include the start time of new dosing regimen with the order.
- Include a range for the predicted concentrations with the new dosage recommendation: (e.g., C_{max} = 30-40 mg/L; C_{tr} 10-20 mg/L).
- Include other pertinent information used to assess the patient: weight (ABW), height, Scr, Clcr, BUN, urine output, I/Os, cultures, T_{max}, WBC, differential, allergies, and other nephrotoxic medications (e.g., furosemide, amphotericin, aminoglycosides).
- Refer to the sample note.

Sample Note

PHYSICAL/HISTORY/
PROGRESS NOTES

Patient Name:
Medical Record:
Date of Birth:

Pharmacy Vancomycin Monitoring Note

Height/Weight: 100kg, 177.8 cm

HPI:

45 YOM with a PMH of IVDU and HTN presents with chest pain, fever, and fatigue. The patient was assessed and worked up for an infection in the ED at UK. Blood cultures were drawn 1 hour ago and a TTE showed a vegetation on the native tricuspid valve. The patient was intubated for airway protection and has been admitted to the MICU. The primary team has asked to start vancomycin for empiric MRSA endocarditis therapy. Scr is pending. Determine the loading dose first and when you would like to obtain your vancomycin concentrations.

Assessment of concs:

Loading dose: 25-30 mg/kg -> 2500 mg IV x 1 dose given over 2.5 hours @0730

Creatinine comes back at 1 mg/dl. You decide to do first-dose kinetics since the patient has MRSA endocarditis and order levels at 2 hours and 10 hours post dose based on the Matzke equation. Use the following concentrations to determine a maintenance dose.

- C1 = 39.5 mcg/mL at 1200
- C2 = 13.5 mcg/mL at 2200

PK parameters: $k = 0.107\text{hr}^{-1}$; $T_{1/2} = 6.46$ hours; $C_{\text{max}} = 48.9$ mg/L; $V_d = 44.9$ L; $Cl = 4.8$ L/h; $TDD_{\text{required}} = 2399.9$ mg; $\tau = 14.45$ hours ~ 12 hours. Predicted C_{max} of 38.5 mg/L and C_{min} of 12.2 mg/L.

Recommendations:

1. Suggest starting vancomycin 1250 mg IV Q12H (12.5 mg/kg/dose). Begin next dose stat since level 2 is <20 mg/L.
2. Recheck a C_{max} & C_{tr} once at steady state (around the 4th dose).
3. Suggest checking Scr/BUN at least 2X/week to assess renal function.

XXXXXX, PharmD
Pager #

Pharmacy Vancomycin Monitoring Note

Height/Weight: 100kg, 177.8 cm

HPI:

45 YOM with a PMH HTN, COPD, and DM presents with 2 days of SOA and productive cough with purulent sputum. He says he was recently admitted a month before for a COPD infection and was given antibiotics. Chest xray on admission is suggestive of pneumonia and he is febrile with a WBC count of $14 \times 10^9/\mu\text{L}$. He is started on piperacillin/tazobactam and vancomycin and admitted to the floor. SCr is 1 mg/dL. The patient's vancomycin dose is 1500mg IV Q12H. A sputum culture obtained on admission is growing *Staphylococcus aureus* with susceptibilities pending. The following concentrations are obtained around the 4th dose at steady state.

Drug levels/Labs-Comments:

C2 = 12.5 mg/L at 1030 (previous dose given on time)
Vancomycin 1500g IV Q12H given at 1100 over 1.5 hours
C1 = 38.8 mg/L at 1430

Assessment of concs:

PK parameters: $k = 0.142 \text{ hr}^{-1}$; $T_{1/2} = 4.90 \text{ hours}$; $C_{\text{max}} = 51.5 \text{ mg/L}$; $C_{\text{min}} = 11.6 \text{ mg/L}$; $V_d = 32.1 \text{ L}$; $\text{AUC}_{24} = 659.8$.

AUC_{24} of 659 is considered supratherapeutic. Can utilize proportions method to determine a new TDD to achieve a goal AUC_{24} of 500. This equates to a TDD of 2276. Recommend to change dose to 1250mg IV Q12H which yields a C_{max} of 47.6 mg/L and C_{min} of 10.3 mg/L and an actual AUC_{24} of 549.

Recommendations:

1. Change dose to vancomycin 1250mg IV Q12H (12.5 mg/kg/dose) to begin at 2300.
2. Not necessary to recheck C_{max} & C_{tr} unless change in clinical status or renal function; if continue therapy > 7 days, would suggest recheck concentrations to assess for drug accumulation.
3. Suggest checking Scr/BUN at least 2X/week to assess renal function.

XXXXXX, PharmD

Pager #

Pharmacy Vancomycin Monitoring Note

Height/Weight: 43 kg

HPI:

RB is a 8 year old male (43 kg) admitted for osteomyelitis of the right foot. Patient was empirically started on vancomycin 750 mg IV every 6 hours. Around the fourth dose, peak and trough concentrations were collected to calculate patient specific pharmacokinetic parameters and evaluate current AUC_{24} .

Drug levels/Labs-Comments:

Dose #4 was given on 3/21 at 0256 as a 60 minute infusion.
Cpk = 35.8 mg/L, collected 3/21 at 0455
Ctr = 11.8 mg/L, collected 3/21 at 0245

Assessment of concs:

PK parameters: $k = 0.29 \text{ hr}^{-1}$; $T_{1/2} = 2.4 \text{ hours}$; $C_{\text{max}} = 47.6 \text{ mg/L}$; $C_{\text{min}} = 11.2 \text{ mg/L}$; $V_d = 16.6 \text{ L}$ (0.39 L/kg); $\text{AUC}_{24} = 623$. Can utilize proportions method to determine a new TDD to achieve a goal AUC_{24} of 400 mg*hr/L. This equates to a TDD of 1925 mg. Could start 480 mg IV every 6 hours targeting the following pharmacokinetic parameters: C_{max} of 30.4 mg/L, C_{min} of 7.1 mg/L and AUC_{24} 400 mg.hr/L. There are other dosing strategies that can be considered as well.

Recommendations:

1. Change to vancomycin 480mg (11.2 mg/kg/dose) IV every 6 hours with next dose starting at 0900.
2. Not necessary to recheck C_{max} & C_{tr} unless change in clinical status or renal function; if continue therapy > 7 days, would suggest recheck concentrations to assess for drug accumulation.
3. Suggest checking Scr/BUN daily to assess renal function.

XXXXXX, PharmD

Epic Secure Chat

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