

Approved: September 2018

VANCOMYCIN DOSING AND MONITORING GUIDELINES (NB Provincial Health Authorities Anti-Infective Stewardship Committee)

GENERAL COMMENTS

- Vancomycin is a glycopeptide antibiotic with bactericidal activity
- It is active against gram-positive bacteria, including methicillin-resistant staphylococcus (MRSA)
- Vancomycin is less effective than beta-lactams against *Staphylococcus aureus* that is susceptible to cloxacillin/methicillin
- Vancomycin exhibits time-dependent killing: its effect depends primarily upon the time the concentration exceeds the organism's Minimum Inhibitory Concentration (MIC)
- These guidelines pertain to IV vancomycin only; they do not apply to PO vancomycin, which is not absorbed
- Ensure that an adequate mg/kg dose and appropriate interval are ordered initially. Adjust the dose if necessary immediately; do not wait for a confirmatory trough level.
- **When managing a severe *Staphylococcus aureus* infection (e.g., bacteremia), an Infectious Diseases consultation is strongly encouraged.**

VANCOMYCIN IN ADULT PATIENTS

ADULT INITIAL DOSE

Loading dose:

- Consider using a loading dose in patients with:
 - severe infections where rapid attainment of target level of 15-20 mg/mL is desired
 - significant renal dysfunction in order to decrease the time required to attain steady state
- **Recommended dose: 25-30 mg/kg IV**
 - based on actual body weight, for 1 dose, followed by maintenance dose separated by recommended dosing interval
 - consider capping the loading dose at a maximum of 3.5 g
 - loading doses DO NOT need to be adjusted in patients with renal dysfunction; only maintenance dosing interval requires adjustment
- If loading dose not used then proceed with administration of a maintenance dose at recommended dosing interval

Maintenance dose:

- **15-20 mg/kg IV**
 - based on actual body weight; maximum of 2g/dose for *initial* maintenance doses (prior to vancomycin levels)
 - doses greater than 500 mg – round to the nearest 250 mg
 - doses less than 500 mg – round to the nearest 50 mg



Dosing interval:

- Interval depends on patient’s renal function and targeted serum vancomycin concentration

Target trough of 15 to 20 mg/L	
Creatinine Clearance	Dosing Interval
greater than 80 mL/min	q8 – 12h
40 to 80 mL/min	q12h
20 to 39 mL/min	q24h
10 to 19 mL/min	q48h
less than 10 mL/min	consider a loading dose, then adjust maintenance dose based on serial serum drug levels to target trough

Target trough of 10 to 15 mg/L	
Creatinine Clearance	Dosing Interval
greater than 80 mL/min	q12h
40 to 80 mL/min	q24h
20 to 39 mL/min	q36h
10 to 19 mL/min	q48h
less than 10 mL/min	consider a loading dose, then adjust maintenance dose based on serial serum drug levels to target trough

- Estimated creatinine clearance (CrCl)

Women	Men
CrCl = $\frac{(140 - \text{age}) \times \text{weight (in kg)}^\dagger}{\text{SCr (in mcmol/L)}}$	CrCl = $\frac{(140 - \text{age}) \times \text{weight (in kg)}^\dagger \times 1.2}{\text{SCr (in mcmol/L)}}$
IBW = 45.5 kg + (0.92 x cm above 150 cm) <i>or</i> 45.5 kg + (2.3 x inches above 60 inches)	IBW = 50 kg + (0.92 x cm above 150 cm) <i>or</i> 50 kg + (2.3 x inches above 60 inches)
†Use ideal body weight unless actual weight is 20% above ideal body weight (IBW), in such case use adjusted body weight. Adjusted body weight = 0.4 x (actual body weight – IBW) + IBW If actual weight is less than ideal body weight, use actual weight.	

Clinical Pearls:

- Use care when selecting patients for q8h dosing – recommend to avoid in patients that are older and/or with multiple co-morbidities (ex. diabetes, heart failure, etc.) or where estimated creatinine clearance would be expected to be an overestimate (ex. low muscle mass in an elderly patient, dysmobility, paraplegia, etc.)
- Consider q8h dosing for patients who are younger and otherwise well with few medical co-morbidities
- The provided ranges for estimated creatinine clearance are only intended to be a guide for the selection of an empiric dosing interval and should not be used in isolation without considering patient and infection-related factors – especially when estimated creatinine clearance approaches either end of the range

LEVELS

- The ratio of Area Under the Curve to Minimum Inhibitory Concentration (AUC/MIC) is thought to be the best pharmacokinetic parameter associated with a clinical and bacterial response to vancomycin; however, because of its relative impracticality to determine in clinical practice, trough levels are used as a surrogate for efficacy.
- Peak (post) levels are generally NOT recommended because they are not correlated with improved clinical outcome; they should only be ordered in rare circumstances to facilitate individualized patient pharmacokinetic analysis.
- Vancomycin’s efficacy depends primarily upon the time above the MIC

Target serum concentrations:

Infection	Desired minimal (trough) plasma concentration
-All MRSA infections -Invasive and/or deep space infections, including but not limited to: <ul style="list-style-type: none"> ○ Osteomyelitis ○ Pneumonia ○ CNS infection ○ Endocarditis ○ Bacteremia ○ Prosthetic joint infection 	15-20 mg/L
Uncomplicated skin and soft tissue infections Urinary tract infections	10-15 mg/L
vancomycin levels should always be maintained above 10 mg/L to avoid development of resistance	

Levels are recommended in:

- patients who are severely ill and/or require target trough of 15-20 mg/L
- patients with anticipated therapy duration of 7 days or greater
- patients with impaired renal function (CrCl 50 mL/min or less) or unstable renal function (change in baseline serum creatinine (SCr) of 40 $\mu\text{mol/L}$ or greater, or change of 50% or more from baseline)
- patients on dialysis
- concomitant use of other nephrotoxic drugs (i.e. aminoglycoside, NSAID, diuretics, ACEI, ARB, etc.)
- patients with altered volume of distribution or clearance of vancomycin, including
 - morbidly obese patients (190% or greater of ideal body weight or BMI 40 kg/m^2 or greater)
 - cystic fibrosis
 - burns more than 20% BSA
 - pregnancy
- Routine trough (pre) levels are generally not necessary when:
 - vancomycin is used for empiric therapy as it may be discontinued once final culture results are available

Serum sampling:

- Trough (pre) levels are taken immediately before a dose (within 30 minutes)
- The timing of drug administration and sample collection must be carefully documented
- Do not hold next vancomycin dose while waiting for results of vancomycin levels unless there is a specific reason to do so, e.g. significant decline in renal function

Timing of serum levels:

- First trough level should be taken at steady state, typically
 - **prior to 4th dose if q12h interval**
 - **prior to the 5th dose if q8h interval**
- Steady state (SS) occurs in 4 to 5 half-lives and can be estimated for vancomycin by the following equations:
 - $K_e = \text{CrCl} \times 0.00083 + 0.0044$
 - $T_{1/2} = 0.693/K_e$
 - $SS = 4 \text{ to } 5 T_{1/2}$
- Vancomycin clearance is enhanced in obesity. Consider drawing first level sooner (i.e. before the 3rd dose if normal renal function) in morbidly obese patients

INTERPRETING TROUGH LEVELS AND ADJUSTING DOSE

- Verify the timing of the trough in relations to the dose that preceded it and the dose that followed
- Verify if the trough was taken at steady state
- Verify for changes in renal function since the trough was drawn
- Consider alternate sources of vancomycin that may be contributing to measured serum concentrations (e.g., vancomycin instilled intra-operatively, or added to cement during orthopedic surgery)
- If the trough is below the target level, ensure the dose is 15-20 mg per kg actual body weight, and consider shortening the dosing interval (e.g., if was dosed q12h, change to q8h)
- If the trough is above 20-25 mg/L, consider decreasing the dose and/or lengthening the dosing interval
- If trough level is significantly elevated (i.e. greater than 30 mg/L) hold vancomycin and use repeat levels to determine when to restart vancomycin and new dosing regimen

MONITORING

Subsequent serum levels:

- With dosage change: trough should be repeated at new steady state as described in “Levels” section
- Once target trough achieved: trough should be taken approximately every 7 days in hemodynamically stable patients; more frequently if hemodynamically unstable, renal function changing, if concurrent nephrotoxic drugs, or underlying renal dysfunction

Monitor:

- patient’s clinical response to vancomycin
- CBC at least weekly on long-term vancomycin therapy
- SCr at least twice a week initially, then at least weekly on long-term therapy; more frequent monitoring should be considered if renal function changing, if concurrent nephrotoxic drug, underlying renal dysfunction or age greater than 60.
 - If SCr increases significantly (i.e. greater than 15 – 20% from baseline), draw trough level to assess for need for dosage adjustment as vancomycin accumulation may occur

Adverse effects of vancomycin include:

- Nephrotoxicity: 5-43%; more common with higher trough levels, longer durations, critically ill patients, concomitant nephrotoxic drugs, elderly patients or pre-existing renal dysfunction; rise in SCr usually reversible upon discontinuation of vancomycin
- Red Man Syndrome: 5-10%; ensure appropriate duration of infusion to minimize risk (refer to Parenteral Drug Manual)
- Neutropenia: less than 2%, delayed onset (15-40 days), reversible

VANCOMYCIN IN PEDIATRIC PATIENTS

DEFINITIONS			
<ul style="list-style-type: none"> • Neonate: 0-4 weeks of age <ul style="list-style-type: none"> ○ Gestational age: number of weeks from first day of the mother's last menstrual period until the birth of the baby ○ Postnatal age: chronological age since birth ○ Corrected Gestational Age: gestational age plus postnatal age Ex.: baby born at 28 weeks, presently 21 days old corrected gestational age = 31 weeks (28 weeks + 3 weeks) • Infant: 1 month to 1 year of age • Child: 1-12 years of age 			
PEDIATRIC INITIAL DOSE			
Initial dose in neonates (less than 1 month of age):			
Corrected Gestational Age (weeks)	Postnatal Age (days)	mg/kg/dose IV	Interval (hours)
29 or less	0-14	10 - 15	18
	15 or more	10 - 15	12
30-36	0-14	10 - 15	12
	15 or more	10 - 15	8
37-44	0-7	10 - 15	12
	8 or more	10 - 15	8
45 or more	all	10 - 15	6
Initial dose in infants and children (1 month to 12 years of age):			
<ul style="list-style-type: none"> • Traditional: <ul style="list-style-type: none"> ○ 40-60 mg/kg/day, divided in q6h-8h ○ max dose of 2g/day prior to levels • Alternative (for more severe infections): <ul style="list-style-type: none"> ○ 15 mg/kg/dose IV q6h ○ max dose of 4g/day prior to levels 			
LEVELS			
<ul style="list-style-type: none"> • Trough levels are taken 30 minutes or less prior to the next dose • Peak levels are generally NOT recommended 			
Target trough levels in neonates (less than 1 month of age):			
<ul style="list-style-type: none"> ○ 5-15 mg/L ○ up to 20 mg/L for severe infections where vancomycin penetration to the site may be poor or high MIC is suspected (osteomyelitis, meningitis and endocarditis or infection with MRSA) 			
Target trough levels in infants and children (1 month to 12 years of age):			
<ul style="list-style-type: none"> ○ 15-20 mg/L for most infections ○ 10-15 mg/L for less severe infections • First trough level should be taken at steady state, typically prior to 4th dose 			
INTERPRETING TROUGH LEVELS AND ADJUSTING DOSE			
<ul style="list-style-type: none"> • Verify the timing of the trough in relations to the dose that preceded it and the dose that followed • Verify if the trough was taken at steady state • Verify for changes in renal function since the trough was drawn • If the trough is below the target level, consider shortening the dosing interval • If the trough is high, consider lengthening the dosing interval 			
SUBSEQUENT TROUGH LEVELS AND MONITORING			
<ul style="list-style-type: none"> • See Adults section for guidance 			

VANCOMYCIN IN INTERMITTENT HEMODIALYSIS

GENERAL COMMENTS
<ul style="list-style-type: none">• In patients undergoing intermittent hemodialysis, vancomycin IV is given on dialysis days, typically 3 times a week• Give the first dose of vancomycin the day it is ordered and subsequent doses on dialysis days• Vancomycin doses are administered during the last portion of the hemodialysis session (intradialytic administration) or after hemodialysis
DOSE
<ul style="list-style-type: none">• Patient with weight less than 70 kg: vancomycin 1000 mg IV for the first dose, then 500 mg IV for subsequent doses• Patient with weight 70 to 100 kg: vancomycin 1250 mg IV for the first dose, then 750 mg IV for subsequent doses• Patient with weight above 100 kg: vancomycin 1500 mg IV for the first dose, then 1g IV for subsequent doses
LEVELS
<p>Target pre-dialysis vancomycin levels:</p> <ul style="list-style-type: none">○ 15-20 mg/L○ 10-15 mg/L may be acceptable for uncomplicated skin and soft tissue infections and urinary tract infections; see Adults section for more information <ul style="list-style-type: none">• Vancomycin levels are drawn before the beginning of the hemodialysis session• Do not hold post-dialysis vancomycin dose while waiting for results of pre-dialysis vancomycin levels unless there is a specific reason to do so• If the trough is below the target level, consider a top-up dose and increase the next maintenance dose accordingly• If the trough is high, consider decreasing the next maintenance dose• Vancomycin trough levels should be obtained before each dialysis until desired trough is attained. After that, vancomycin trough levels should be obtained once a week before dialysis.

VANCOMYCIN IN PREGNANCY

CONSIDERATIONS ON THE USE OF VANCOMYCIN IN PREGNANCY

- Pregnancy is associated with accelerated renal clearance of vancomycin due to increased renal blood flow
- Pregnancy is associated with higher volumes of distribution
- Pharmacokinetic changes become more pronounced in the later stages of pregnancy and gradually return to pre-pregnancy values a few days following delivery
- Dose and target trough levels same as other adults
- Will likely achieve steady state sooner
- May require higher dosage and shorter dosing intervals to achieve target levels compared to non-pregnant individuals
- Recommend routine trough levels in pregnant patients
- If target levels difficult to achieve, consider drawing two levels (trough and peak) to enable individualized pharmacokinetic calculations

OUTPATIENT VANCOMYCIN IV THERAPY

NOTES FOR TRANSITIONS TO OUTPATIENT IV VANCOMYCIN THERAPY

- Prior to discharge on outpatient IV vancomycin therapy, the healthcare team should:
 - Review the treatment plan to confirm that oral alternatives are not available or appropriate for patient management
 - Review the feasibility and safety of the treatment and care plan
 - Review the patient's concomitant medications to identify any nephrotoxic agents (e.g. aminoglycoside, NSAID, diuretic, ACEI, ARB, etc.) and evaluate whether any should be held for the duration of treatment
 - Communicate the treatment and care plan to the patient and/or care givers and community healthcare providers; including necessary blood work, target levels and duration of therapy
 - Communicate the importance of proper timing of blood work in relation to administration of the vancomycin dose to allow interpretation of vancomycin serum concentrations
 - Educate and inform the patient and their caregivers on the signs and symptoms of potential adverse reactions to report or act on
 - Arrange all necessary monitoring test and follow-up appointments
 - Avoid scheduling blood work on Fridays because interpretation may be delayed

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