

Amended: October 2020

## 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 10-15 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 3g
  - 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 10 to 15 mg/L	
Creatinine Clearance	Dosing Interval
greater than 80 mL/min	q8-12h
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
$CrCl = \frac{(140 - \text{age}) \times \text{weight (in kg)}^\dagger}{SCr \text{ (in mcmol/L)}}$	$CrCl = \frac{(140 - \text{age}) \times \text{weight (in kg)}^\dagger \times 1.2}{SCr \text{ (in mcmol/L)}}$
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:**

- After a thorough review of the available evidence, NB-ASC recommends a **target trough level of 10-15 mg/L** for **ALL** infections.
  - There is no reliable data to support the use of a target trough of 15-20mg/L.
  - However, there is data demonstrating that target troughs of 15-20 mg/L are associated with greater risk of nephrotoxicity.
- Vancomycin levels should always be maintained above 10 mg/L to avoid the development of resistance.

**Levels are recommended in:**

- patients who are severely ill
- 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 mcmol/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<sup>2</sup> 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 4<sup>th</sup> dose if q12h interval**
  - **prior to the 5<sup>th</sup> dose if q8h interval**
- Steady state (SS) occurs in 4 to 5 half-lives and can be estimated for vancomycin by the following equations:
  - $K_e = CrCl \times 0.00083 + 0.0044$
  - $T_{1/2} = 0.693/K_e$
  - $SS = 4 \text{ to } 5 T_{1/2}$
- Vancomycin clearance is enhanced in obesity. Consider drawing first level sooner (i.e. before the 3<sup>rd</sup> 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 15-20 mg/L, consider decreasing the dose and/or lengthening the dosing interval
- If trough level is significantly elevated (i.e. greater than 25 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**

- **Neonate:** 0-4 weeks of age
  - 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):**

- Traditional:
  - 40-60 mg/kg/day, divided in q6h-8h
  - max dose of 2g/day prior to levels
- Alternative (for more severe infections):
  - 15 mg/kg/dose IV q6h
  - max dose of 4g/day prior to levels

<b>LEVELS</b>
<ul style="list-style-type: none"> <li>• Trough levels are taken 30 minutes or less prior to the next dose</li> <li>• Peak levels are generally NOT recommended</li> </ul>
<p><b>Target trough levels:</b></p> <ul style="list-style-type: none"> <li>○ 5-15 mg/L for highly susceptible infections (e.g. coagulase negative Staphylococci bacteremia)</li> <li>○ 10-15 mg/L for methicillin susceptible <i>Staphylococcus aureus</i> (MSSA) infections or MRSA</li> <li>○ Higher exposure may be required for other syndromes such as CNS infections, endocarditis, osteomyelitis and other deep seated MRSA infections: <ul style="list-style-type: none"> <li>▪ Pre (trough) levels could therefore be targeted close to 15 mg/L (i.e. 13 – 15 mg/L)</li> <li>▪ Pre (trough) levels that exceed 15 mg/L are associated with an increased risk of nephrotoxicity.</li> </ul> </li> </ul> <ul style="list-style-type: none"> <li>• First trough level should be taken at steady state, typically <b>prior to 4th dose</b></li> </ul>
<b>INTERPRETING TROUGH LEVELS AND ADJUSTING DOSE</b>
<ul style="list-style-type: none"> <li>• Verify the timing of the trough in relations to the dose that preceded it and the dose that followed</li> <li>• Verify if the trough was taken at steady state</li> <li>• Verify for changes in renal function since the trough was drawn</li> <li>• If the trough is below the target level, consider shortening the dosing interval</li> <li>• If the trough is high, consider lengthening the dosing interval</li> </ul>
<b>SUBSEQUENT TROUGH LEVELS AND MONITORING</b>
<ul style="list-style-type: none"> <li>• See Adults section for guidance</li> </ul>

## VANCOMYCIN IN INTERMITTENT HEMODIALYSIS

<b>GENERAL COMMENTS</b>
<ul style="list-style-type: none"> <li>• In patients undergoing intermittent hemodialysis, vancomycin IV is given on dialysis days, typically 3 times a week</li> <li>• Give the first dose of vancomycin the day it is ordered and subsequent doses on dialysis days</li> <li>• Vancomycin doses are administered during the last portion of the hemodialysis session (intradialytic administration) or after hemodialysis</li> </ul>
<b>DOSE</b>
<ul style="list-style-type: none"> <li>• <b>Patient with weight less than 70 kg:</b> vancomycin 1000 mg IV for the first dose, then 500 mg IV for subsequent doses</li> <li>• <b>Patient with weight 70 to 100 kg:</b> vancomycin 1250 mg IV for the first dose, then 750 mg IV for subsequent doses</li> <li>• <b>Patient with weight above 100 kg:</b> vancomycin 1500 mg IV for the first dose, then 1g IV for subsequent doses</li> </ul>
<b>LEVELS</b>
<p><b>Target pre-dialysis vancomycin levels:</b></p> <ul style="list-style-type: none"> <li>○ 10-15 mg/L for ALL infections</li> </ul> <ul style="list-style-type: none"> <li>• Vancomycin levels are drawn before the beginning of the hemodialysis session</li> <li>• 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</li> <li>• If the trough is below the target level, consider a top-up dose and increase the next maintenance dose accordingly</li> <li>• If the trough is high, consider decreasing the next maintenance dose</li> <li>• 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.</li> </ul>

## 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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