



Vancomycin Therapeutic Drug Monitoring Vancouver Coastal Health & Providence Health Care Regional Guideline

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Background

At VCH-PHC, vancomycin therapeutic drug monitoring practice varies considerably between the sites. This variance reflects the differences in institutional recommendations for indications for serum level monitoring and how pharmacists respond to these levels. This diversity is in part due to poor quality evidence that links specific levels to improved outcome.

Currently, at certain sites pharmacists can spend a considerable amount of time evaluating vancomycin serum levels. These levels are associated with significant costs (pharmacist time, patients' blood loss, and laboratory costs). Therefore, there is an opportunity to both optimize the pharmacists' time for other clinical activities and reduce costs associated with unnecessary laboratory tests.

This guideline aims to identify the "best clinical practice" for vancomycin monitoring by defining indications for ordering vancomycin serum levels and providing guidance on how levels should be evaluated. Essential factors that are being considered include the pharmacokinetic and pharmacodynamic properties of vancomycin, the evidence for target levels and its association with efficacy and toxicities, the MIC of the target pathogens, and the expected patient benefit from a precise pharmacokinetic evaluation.

Goals

Application of "best clinical practice" across sites should achieve the following goals:

- Reduce the number of vancomycin serum levels routinely ordered when either:
 - a level less than 15 mg/L is targeted **OR**
 - a post level is ordered to determine precise pharmacokinetic parameters.
- Increase the pharmacists' time for other clinical activities.

Objectives

To provide recommendations for:

1. Target vancomycin serum levels for specific indications and pathogens.
2. Indications for levels:
 - 2.1: a pre-level only is required
 - 2.2: post-levels are required
 - 2.3: pre- and post-levels set is required.
3. Evaluation of patients not clinically responding.
4. Dosing strategies for “low level ~ 10 mg/L” and “high level 15 to 20 mg/L” targets.

General Recommendations

These recommendations provide guidance to vancomycin dosing and monitoring. The pharmacist may use their professional judgment in patient-specific scenarios and deviate from these recommendations if deemed clinically appropriate.

Unless otherwise stated, the term “level” refers to the “pre-level.”

- Target levels may be categorized as: low level (~ 10 mg/L) and high-level (15 to 20 mg/L), reflecting different target pathogens and infection sites.
- It is important to ensure that an adequate mg/kg dose and interval are ordered, as soon as the patient is reviewed and to adjust the regimen if necessary rather than to wait for a confirmatory pre-level.
- For patients under 40 years of age with good renal function, the dosing interval should be adjusted to Q8H; for dosing protocols that use a 25 mg/kg load with a 15 mg/kg maintenance dose Q12H would generally achieve levels close to 10 mg/L.
- A dosing nomogram designed to achieve high target levels of 15 to 20 mg/L has been developed and validated.
- The use of a serum creatinine value post fluid resuscitation is recommended rather than relying on the initial serum creatinine that is reported on admission or immediately post-operatively (which may be elevated pre-resuscitation).
- Serum creatinine may not be a reliable marker of renal function in some populations, such as the frail elderly, nutritionally deficient, anorexic, or HIV population. In these populations estimations of dosing interval should be based on age and a conservative approach to selecting the interval (selection of a less frequent dosing regimen than suggested by the creatinine).
- Changes in serum creatinine may be helpful in detecting/predicting vancomycin accumulation. Relative increase of greater than 15-20% from baseline (regardless of whether or not the creatinine is in the normal range) may indicate a decline in renal function significant enough to cause vancomycin accumulation. Such changes may warrant a vancomycin pre-level.

Specific Recommendations

1. Target vancomycin levels for specific indications and pathogens

Table 1. Target vancomycin pre-levels for specific indications

<p>Conditions requiring pre-levels 15 mg/L to 20 mg/L (high-level) Catheter-associated bacteremia CNS infection Deep-seated or sequestered infection (e.g. abscess) Endocarditis Osteomyelitis MRSA bacteremia, pneumonia, or skin and soft tissue infection MSSA bacteremia (penicillin allergic patient)</p> <p>Conditions requiring pre-levels ~ 10 mg/L (low-level) Skin and soft tissue infection not due to MRSA Urinary tract infection (catheter-associated; rule out bacteremia)</p>

<http://www.idsociety.org/content.aspx?id=4434#mcrid>

2. Indications for levels

2.1 Pre-Levels

- a. Pre-vancomycin level drawn no earlier than the 3rd dose and within 48 hours or as per clinical judgment if:
- a higher level of 15-20 mg/L is desired OR
 - patient is at risk for accumulation (e.g. Q8H interval) OR
 - patient is receiving other nephrotoxic agents OR
 - serum creatinine is above normal, renal function is changing or uncertain OR
 - patient is obese (>125% IBW) (Appendix 1), pregnant (Appendix 2), pediatric (0-18 years of age) (Appendix 2), or hypermetabolic (e.g. burn patient, cystic fibrosis).

Repeat at least weekly to ensure pre-vancomycin level is within desired therapeutic range. Clinical judgment may be used here especially for prolonged vancomycin courses where 2-3 pre-levels over the course of 2-3 weeks have been within target providing regular (2-3X week) serum creatinine ordered.

- b. Pre-vancomycin level after 7 days of therapy (for prolonged course) if aiming for levels < 15 mg/L AND no other risk factors as per above.
- c. Pre-vancomycin level if patient is not responding to therapy.

2.2 Post-Levels

a) Stable but impaired renal function

- Load patients with 20 to 25 mg/kg of vancomycin.
- Patients with stable renal function and CrCl less than 24 mL/min:
 - Order two post-distributional levels typically 3 hours and 24 hours post dose or as per clinical pharmacist judgement.
- Patients with an estimated CrCl of 24 to 48 mL/min:
 - Empirically dose at a Q36H to Q48H interval **AND** obtain a single pre-level for these patients at an appropriate time to identify if adjustments in the regimen are required **OR**
 - At sites where this is not yet routine practice, can order 3 hours and 24 hours levels then interpret and adjust regimen.

b) Acute unstable renal function.

- All patients should receive an appropriate loading dose of 25 mg/kg (or 30 mg/kg if critically ill in the ICU).
- Subsequent dosing can be guided by performing random levels timed appropriately (usually close to the time when a repeat dose may be needed) to allow repeat dosing to maintain levels within the desired target until the renal function stabilizes.

2.3. Pre and Post-levels

Pre- and post-levels are not routinely recommended.

- Pre- and 3 hour post-vancomycin level (target 20-40 mg/L) should be drawn if calculation of precise kinetic parameters are necessary (e.g. in a case when a target pre-vancomycin level of 15-20 mg/L cannot be achieved while on prolonged therapy, or in an obese, pregnant or pediatric patient (Appendix 2), especially when aggressive dosing
- It is not recommended to perform routine pre- and post-levels for endocarditis, meningitis, and life-threatening conditions to establish kinetic parameters. Rather, it is recommended that for these indications the pharmacist focus immediately on ensuring appropriate adjustments of dose and or interval to ensure rapid attainment of a pre-level of 15 mg to 20 mg/L within 48 hours and to use their judgment to subsequently adjust the doses and or intervals.

2.4 Two Post-levels

For patients with unstable or reduced renal function, the clinical pharmacist should assist in determining the appropriate dosing regimen. These patients may require a loading dose and subsequent post-levels (e.g. 3 hour and 24 hour post-dose serum levels) to ensure therapeutic serum levels are achieved.

3. Evaluation of patients not clinically responding

3.1 Evaluation of a pre-level in patients not clinically responding when target is low-level ~10 mg/L

- In general, if the patient is receiving adequate mg/kg dosing and interval based on the age, weight and serum creatinine for low target levels, monitoring is not needed for the first 7 days. However, if a lack of clinical response cannot be explained by other factors, the regimen should be adjusted to ensure the level is increased to a high level target of 15 mg/L to 20 mg/L and a pre-level taken to confirm that the target is reached.

3.2 When the target level of more than 15 mg/L has been achieved

If the patient is not responding clinically (especially if the organism is repeatedly isolated), this may signal that the MIC is close to 2 mg/L. Higher levels (20 to 25 mg/L) may be needed. This is particularly important if the target site is sequestered. If available, an Infectious Disease consult is recommended and/or consideration of alternative or additional agents is warranted.

4. Dosing strategies for low and high levels

Adult dosing recommendations

The emphasis should always be on providing an initial correct dose and interval following the nomogram. (Table 1).

Table 2. Vancomycin empiric dosing guidelines

**VCH-PHC Vancomycin Empiric Dosing Guidelines
(June 2011)**

Vancomycin Empiric Dosing Guidelines

TOTAL BODY WEIGHT	LOADING DOSE (maximum 2500 mg/dose)		MAINTENANCE DOSE (15 mg/kg)
	Target pre-level 10-15 mg/L (20 mg/kg)	Target pre-level 15-20 mg/L (25 mg/kg)	
kg			
40-50	1000 mg	1250 mg	750 mg
51-60	1250 mg	1500 mg	1000 mg
61-70	1250 mg	1750 mg	1000 mg
71-80	1500 mg	2000 mg	1250 mg
81-90	1750 mg	2250 mg	1250 mg
91-100	2000 mg	2500 mg	1500 mg

SUGGESTED TARGET PRE-VANCOMYCIN LEVELS BASED ON INDICATION

Pre-vancomycin Level 10-15 mg/L	Pre-vancomycin Level 15-20 mg/L
<ul style="list-style-type: none"> • Skin and soft tissue infection <u>not</u> due to MRSA • Urinary tract infection (catheter-associated; rule out bacteremia) 	<ul style="list-style-type: none"> • Catheter-associated bacteremia • Central nervous system infection • Deep-seated or sequestered infection (e.g. abscess) • Endocarditis • Osteomyelitis • MRSA bacteremia, pneumonia or skin and soft tissue infection • MSSA bacteremia (penicillin allergic patient)

LOW-TARGET 10-15 mg/L INITIAL DOSING INTERVAL (hours)

SCr (mcmol/L)	Age Group (years)					
	20-29	30-39	40-49	50-59	60-69	70-79
40-60	8	8	12	12	12	18
61-80	8	12	12	12	18	18
81-100	12	12	12	18	18	18
101-120	12	12	18	18	18	24
121-140	12	18	18	18	24	
141-160	18	24	24	24		
161-180	24	24				
181-200	24					

HIGH-TARGET 15-20 mg/L INITIAL DOSING INTERVAL (hours)

SCr (mcmol/L)	Age Group (years)						
	20-29	30-39	40-49	50-59	60-69	70-79	80-89
40-60	8	8	8	8	8-12*	12	12
61-80	8	8	8-12*	12	12	12	12-18*
81-100	12	12	12	12	12-18*	18	18
101-120	12	12	12-18*	18	18	18	18
121-140	12	18	18	18	18	18-24*	
141-160	18	18	18	18-24*	24		
161-180	18-24*	24	24	24			

*If more aggressive therapy is desired, select more frequent dosing interval.

Shaded boxes: These patients have unstable and/or reduced renal function, and the nomogram may not be as predictive.
 • A clinical pharmacist should be contacted for assistance with dosing and interpretation of levels.

Dosing recommendations for children and pregnant women (see Appendix 2)

Further information explaining the rationale behind the recommendations is provided in Appendix 3.

Appendix 1 Dosing Recommendations for Obese Patients

The formal definition of obesity is defined as a BMI of 30 or more. To facilitate weight-based drug dosing (not BMI), the following method is used to calculate the ideal body weight.

- Actual body weight is recommended when dosing obese patients. The usual maximum dose is 2.5 g per dose.
- A pre-level is recommended when a patient is 125% or more greater than the IBW. These patients may have altered kinetic parameters and require Q8H dosing to ensure that an adequate pre-level is achieved.

Estimated ideal body weight in kg

Males: $IBW = 50 \text{ kg} + 2.3 \text{ kg for each inch over 5 feet.}$

Females: $IBW = 45.5 \text{ kg} + 2.3 \text{ kg for each inch over 5 feet.}$

Appendix 2

Dosing Recommendations for Children and Pregnant Women

For pediatric patients, the Children's and Women's Hospital of British Columbia dosing guidelines recommend routine empiric vancomycin doses of 40-60 mg/kg/day, divided every 8 hours. For meningitis, 60 mg/kg/day divided every 6 hours is recommended.

The upper end of the routine dosing range would be appropriate when more aggressive dosing is indicated, i.e. target pre levels of 15-20 mg/L. For neonates (infants up to 28 days of age), 15 mg/kg/dose is given at intervals adjusted for gestational age. (Please consult the Neonatal Dosing Guidelines section of the current edition of the BCCH Pediatrics Drug Dosage Guidelines).

Pediatric patients with normal renal function may have accelerated clearance of vancomycin, and very young children may have higher distribution volumes per kg body weight than older children and adults. For these reasons, it is appropriate to draw a pre-level routinely at the third dose to ensure that the target level is achieved. Dosing every 6 hours may be required in some pediatric patients, especially when aiming for pre-levels of 15-20 mg/L.

Post-levels may be required if target pre-levels have been difficult to achieve. Calculating kinetic parameters may clarify the need for increased dose in addition to a shorter dosing interval. Also, kinetic parameters may be useful for dosing interval adjustments in pediatric patients with stable but impaired renal function, as estimates of creatinine clearance from serum creatinine in pediatric patients may be less reliable.

Patients who are pregnant and have normal renal function may also have accelerated clearance of vancomycin due to increased renal blood flow in pregnancy. They are also likely to have higher distribution volumes due to increased blood volume, among other factors. These effects become more pronounced in the later stages of pregnancy, and persist (but gradually return to pre-pregnancy values) over the first few days post-partum. It is appropriate to use usual adult mg/kg doses and nomograms for initial dosing intervals. However, pre-levels should be drawn at the third dose, and consider post-levels and estimation of kinetic parameters if shorter dosing intervals do not achieve target levels.

Appendix 3 Additional Information and Rationale Behind the Recommendations

Pre-level only vs. pre- and post-levels to assess efficacy?

- Vancomycin exhibits time-dependent bacterial killing.
- AUC/MIC is the parameter that is most closely associated with efficacy in neutropenic mouse models¹ and in one clinical study of MRSA/MSSA pneumonia².
 - A pre-level is the best surrogate marker for AUC/MIC.
 - Therefore, post levels are not required to assess efficacy.

Pre-levels for all patients to ensure efficacy?

- Historical dosing guidelines were designed to achieve pre levels of ~10 mg/L in adult patients with “normal” distribution characteristics.
 - Confirmatory pre-levels are not needed if the target is 10 mg/L to 15 mg/L if treatment duration is less than 7 days.
- But, some infections require a target more than 15 mg/L (based on current standards of practice and animal or *in-vitro* data).
 - The VCH-PHC High Target nomogram should be used to dose these patients.
 - However, given the indications for high targets (typically invasive infections, involving drug resistant organisms), there is a need to confirm/ assess efficacy with a therapeutic pre-level.

What is the evidence that targeting more than 15 mg/L is needed?

- AUC/MIC 400 is associated with optimal response in patients with MRSA/MSSA pneumonia using modeled AUC data².
- For isolates with MIC of 1 mg/L, this is achieved with serum levels of 20 mg/L (AUC 300 (10 mg/L); 350 (15 mg/L)).
- But for isolates with MIC 2 mg/L (susceptibility breakpoint is more than 2 mg/L), an AUC/MIC 400 will not be achieved. This may be the reason that isolates with MIC 2 mg/L cannot be adequately treated with pre-levels of 15 mg/L to 20 mg/L, as demonstrated in clinical studies.
- Although a retrospective study did not show an association between pre-levels more than 15 mg/L and improved outcome for MRSA pneumonia (the MIC's were not reported)³. These results could be explained by the fact that the authors did not consider the AUC and MIC when assessing the outcomes.
- Achieving pre-levels of free (unbound) vancomycin of 4-5 times the MIC of the pathogen was another method used in one clinical study. If protein binding is assumed to be 50%, this would require pre-levels of 16 to 20 mg/L. This does not take into consideration that higher levels are needed to penetrate sequestered sites (e.g. pneumonia).

- Two clinical studies reporting MIC's show that response differs significantly if the MIC is high (2 mg/L) for MRSA pneumonia ± bacteremia⁴ and MRSA bacteremia⁵ vs. low (less than or equal to 1 mg/L).
- Development of resistance on therapy has been found in *Staphylococcus aureus* bacteremia when a target level of only 10 mg/L was achieved.

Bacteremia due to MSSA or MRSA

- Levels greater than 10 mg/L are recommended to reduce the likelihood of vancomycin intermediate strains of *Staphylococcus aureus* developing while on therapy.
- There is data to suggest an increase in mortality if the pre-level is 10 mg/L and the MIC is close to 2 mg/L (2 mg/L is susceptibility breakpoint).
- For isolates of MRSA from blood (VCH data):
 - 37% MIC less than 1.5 mg/L
 - 63% MIC more than 1.5 mg/L less than 2 mg/L.
- For isolates of MSSA, the MIC grouping is not known.
- It should be noted that determination of MIC for MRSA is somewhat subjective and results should be interpreted with caution.
- Therefore, for bacteremia due to MSSA or MRSA, a pre-level of 15 mg/L is recommended. Bacteremia with these organisms is likely to occur in the setting of pneumonia or endocarditis.

When is a pre-level of ~10 mg/L adequate?

- UTI's due to CoNS should be adequately treated with these levels. This is because vancomycin is renally eliminated, so a higher AUC/MIC in the bladder will be achieved.
- Skin and soft tissue infections
 - Patients with these infections may require higher pre-levels:
 - Diabetics with compromised vascular supply may potentially have reduced drug delivery to the target site
 - Recurrent infection with possibly increasing MIC.
 - Higher pre-levels more than 15 mg/L would be needed if MRSA is suspected.

Is a post-level needed to establish individual pharmacokinetic parameters so that dosing can be optimized?

- Precise knowledge of an individual's kinetic parameters (i.e. Vd and Ke) should not be needed because a pre-level should be sufficient to guide dosing when the target is more than 15 mg/L.
 - Many patients could be at or near 15 mg/L that clinical judgment alone should be all that is required to achieve target level.
 - Precise kinetic estimates are somewhat "muted" by relatively fixed increments in dose (250 to 500 mg increments) and interval (intervals of Q8H, Q12H, Q18H, etc). For pediatric patients, doses are usually calculated in 10 mg increments, e.g. 220 mg IV q8h for an 11 kg child.

- Precise knowledge may be useful if levels of more than 15 mg/L have not been achieved despite empiric adjustment and the pharmacist needs to have this additional information in order to recommend a regimen.
 - However, this situation would be expected to occur very rarely and only in patients with serious infections with a prolonged anticipated duration, (e.g. endocarditis or meningitis), or in patients with rapid renal elimination and/or potentially larger distribution volumes, (e.g. in pregnancy or in pediatric patients).
 - It is much more important for the patient to receive an appropriate mg/kg initial dosing – up to 30 mg/kg and interval to achieve early target levels, as toxicity is not likely to occur. A repeat pre level at 7 days can be done to ensure no accumulation occurs beyond 25 mg/L.

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