VANCOMYCIN

A. KINETIC PARAMETERS[1]

Protein Binding	55%
Vd	0.5 - 1 L/kg (Average: 0.7 L/kg)
Elimination Half Life	30-60 minutes for distribution phase Terminal elimination phase: **ADULTS:** 7 - 9 hours 20 - 140 hours in end stage renal disease (ESRD) 4 hours in severe burns 3 – 4 hours in obesity **PEDIATRICS:** Newborns: 6-10 hours 3 months to 4 years: 4 hours > 3 years: 2.2-3 hours
Elimination	Renal: 80-90% unchanged Non-renal elimination only of note in ESRD
Suggested target ranges (Trough)	10 – 20 mg/L 15 - 20 mg/L for serious/complicated infections such as pneumonia due to *S. aureus*, bacteremia, endocarditis (IE), osteomyelitis, or meningitis[2]
(Peak)	Very little evidence supports the use of peak levels; however, where pharmacokinetic calculations are necessary (e.g. some pre-term neonates), where clinical judgement suggests highly variable pharmacokinetics, post/peak levels may be appropriate to facilitate patient specific kinetic calculations.

B. DOSING IN ADULTS:

1. Dose:

- 15 mg/kg/dose based on **actual body weight** (ABW)
  - Doses > 500 mg – round to nearest 250 mg
  - Doses < 500 mg – round to nearest 50 mg
- Maximum initial dose (before adjusted with levels) is 2 g/dose (excludes loading dose)
- Administer over 60 -120 minutes

Loading Dose:

- Recent guidelines for vancomycin TDM[2] have recommended inclusion of loading doses for patients with severe infections where rapid achievement of target trough levels of 15-20 mg/L is required. This may include infections such as septic shock, epidural abscess, vertebral osteomyelitis, or necrotizing MRSA pneumonia.
- There may be benefit in a loading dose for patients with significant renal function impairment in order to reduce the time required to achieve target trough levels.
- If used, recommended loading dose is 25-30 mg/kg (actual body weight) as single dose followed by dose as calculated above separated by recommended dosing interval (e.g. 8 or 12 h later).

Dosing in Intermittent Hemodialysis (IHD):[3,4,5,6]

- For patients on peritoneal dialysis (PD) or IHD with a low flux filter consider a loading dose of 25-30 mg/kg as the first dose (see above). Further dosing should be based on follow up levels, but expect a dosing interval of 7-10 days.
- For patients on high flux IHD, consider a loading dose of 25 mg/kg (max 2000 mg) followed by "top up" dosing of 500-750 mg of vancomycin with each of the following dialysis runs. These doses should be infused over the last 60-120 minutes of the dialysis run (depending on how long the dose is to infuse).
    - For patients with vancomycin targets of 10-15 mg/L – give 500 mg
    - For patients with vancomycin targets of 15-20 mg/L – give 750 mg unless the patient is < 60 kg in which case 500 mg is sufficient.

2. Initial Dosing Interval:

i) Estimate patient's creatinine clearance (see appendix).

ii) Calculate initial dosing interval based on estimated creatinine clearance:

$ke_{(vancomycin)} = 0.00083 * CrCl + 0.0044$

$$\text{Ideal Dosing interval} = \frac{\ln(C_{max}/C_{min})}{ke_{(vancomycin)}}$$

NB: For Cmax suggest using value between 30-40 mg/L as this was traditionally considered target peak range.[1]

OR

Choose initial dosing interval based on chart*:

Calculated CrCl (mL/min)	Dosing Interval for targets 10-20 mg/L	Dosing Interval for targets 15-20 mg/L
≥ 80	q 12 h	q 8 h
40 - 80	q 24 h	q 12 h
20 - 40	q 36 h	q 24 h
10 - 20	q 48 h	q 48 h
< 10 or in patients on dialysis (e.g. PD, IHD or CRRT)	Consider loading dose and predict ongoing dosing based on estimated k_e calculation above. Follow up vancomycin levels required for confirmation of predictions.	Consider loading dose and predict ongoing dosing based on estimated k_e calculation above. Follow up vancomycin levels required for confirmation of predictions.

* Based on modified nomogram from Bugs & Drugs (2006) – updated to achieve target troughs of 15-20 mg/L. Note this modified nomogram has not yet been validated (2010).

B. DOSING IN PEDIATRICS:

Neonates ≤ 44 weeks Post-Conceptional Age (PCA)

- INITIAL DOSE: 15 mg/kg/dose q 8-24h depending on the gestational age, post-natal age, post-conceptional age and/or weight of the neonate. Refer to local dosing references for local practice.
- If renal dysfunction is suspected (i.e. SCr > 65 mcmol/L or urine output (UO) < 1 mL/kg/h), extend dosing interval and adjust according to trough levels.

Infants and Children

- Children > 44 weeks up to 12 years: Initiate therapy at 60 mg/kg/day, divided q6-8h

- Children/Adolescents > 12 years: As children transition through adolescence (13 years or more) their pharmacokinetic parameters will also change to become increasingly like those of the adult population. Consideration of the age of the child and the severity of illness needs to be made when choosing an initial dose between 40-60 mg/kg/day as well as how that dose would be divided into a q6h, q8h, or q12h interval.

IF YOU ARE UNSURE ABOUT DOSING AND MONITORING THIS MEDICATION PLEASE CONTACT YOUR LOCAL CHILDREN'S HOSPITAL PHARMACY FOR ASSISTANCE.

C. MONITORING

Not all patients on vancomycin require therapeutic drug level monitoring.
Pre-dose (trough) levels may be considered in following conditions:

- Deteriorating/unstable renal function (i.e. increase in baseline SCr of at least 40 mcmol/L or 50% baseline)
- Morbidly obese patients (> 190% IBW)
- Patients with altered volume of distribution or clearance of drug (e.g. cystic fibrosis, pediatrics, elderly patients > 60 years, cancer, burns > 20% BSA)
- Patients on vancomycin ≥ 7 days
- In patients requiring higher target troughs (15-20 mg/L) of vancomycin to penetrate the site of infection or to manage difficult to treat infections (e.g. CNS, endocarditis, pneumonia, osteomyelitis, MRSA infections)
- In patients who are severely ill (i.e. sepsis)
- Selected dialysis patients (e.g. intermittent hemodialysis, or continuous hemodialysis/filtration (CAVH, CVVH, CVVHDF))

Post (peak) levels are generally NOT needed because:

- Vancomycin does not exhibit concentration-dependent killing (as in aminoglycosides); AUC_{24h}/MIC correlates best with clinical outcome and bacterial eradication
- Vancomycin distributes slowly into peripheral tissues, making it difficult to identify the true peak
- There is no correlation with improvements in clinical outcome
- Doing unnecessary levels results in added cost to patient care (> $50/level)
- Post levels may be of value in rare circumstances, where the pharmacist may need to determine patient specific pharmacokinetic parameters.

Sampling times:

- Pre-dose (trough) vancomycin level should only be ordered if patient meets inclusion conditions listed above
- Draw level 30 minutes or less before next dose
    - First level at steady state (3-5 half lives – *not necessarily the same as 3-5 doses*) which is after 24-30 hours in patients with normal renal function.
    - Where possible, avoid drawing levels with nighttime doses as this creates unnecessary patient disturbances.
    - Once target trough level achieved on **steady state dosing regimen**, subsequent levels approximately every 7-10 days (may need more frequently if renal function changing or concurrent nephrotoxic drugs)
- **Pediatrics:** draw pre-dose level before 5th or 6th dose
    - For neonates, patients with a GFR < 80 mL/min/1.73m^2 or those on concomitant nephrotoxic medications consider checking pre-level earlier to ensure levels are not excessive.
    - Vancomycin pre-levels, serum creatinine and urea should be routinely checked every 5 to 7 days in stable patients

- Intermittent hemodialysis (IHD) with high flux filters – draw pre-dialysis serum vancomycin level before 3rd and 4th dialysis runs. If levels remain within target range, may reduce frequency of vancomycin levels to weekly (or less if stable)[7]. If changes are required, recheck levels on new dosing regimen with 3rd and 4th dialysis runs following change, until target troughs maintained.

- IHD with low flux filters (not often used anymore), or peritoneal dialysis – expect negligible vancomycin removal so infrequent dosing and levels required.
- Routine monitoring of peak levels is not required

Dosage Regimen Adjustments in ADULT and PEDIATRICS after Steady State Vancomycin Level:

- Doses should always be rounded to the nearest 250 mg for doses greater than 500 mg and to nearest 50 mg for doses less than 500 mg (excluding pediatric patients).
- Vancomycin follows first order kinetics so new dose can be estimated by comparing with the previous (steady state) dose and level achieved (see calculation below).
- Optimizing target trough may involve shortening the dosing interval and not changing the interval dose, which is why calculation looks at total vancomycin administered/day and not per dose.

$$\text{New vancomycin dose/day} = \frac{\text{Vanc(dose)} * \text{Level(target)}}{\text{Level(actual)}}$$

where: Vanc(dose) = Current Vancomycin dose/day (at steady-state)
Level(target) = Desired target trough level (i.e. 10 – 20 mg/L)
Level(actual) = Measured steady-state trough level

Other Monitoring Parameters

- **Toxicity:**
  - Infusion related reactions – monitor for histamine associated "Red Man Syndrome"
    - Need to differentiate from allergic rash (which will not clear with slower infusion rates and requires drug discontinuation)
  - Serum creatinine
    - Baseline and at least once weekly (more frequently if changing renal function or concurrent nephrotoxic drugs)
    - If creatinine changes (increase of > 40 mcmol/L or 50% of baseline), suggest drawing a trough vancomycin level to assess need for dosing change
  - Complete blood count with differential (looking for vancomycin associated neutropenia or thrombocytopenia on rare occasions)
    - Baseline and at least once weekly on prolonged therapy

4) Factors Affecting Patient Response

Decreased clearance *Increased vancomycin concentration*	Increased clearance *Decreased vancomycin concentration*
renal impairment	burn patients obesity IV drug user hematologic malignancy

D. TOXICITY

1) Dose related

Nephrotoxicity

- Defined in the literature as an increase in serum creatinine of 40-50 mcmol/L or 50% increase from baseline (whichever is greater) on 2 consecutive occasions at any time during vancomycin therapy
- Increased risk with concurrent therapy with nephrotoxic agents (aminoglycosides, amphotericin B, loop diuretics, vasopressor agents, contrast dyes, ACE inhibitors, etc.),
- Risk of nephrotoxicity increases once trough concentrations exceed 20 mg/L[1]

Ototoxicity

- Ototoxicity reports were with initial formulation of vancomycin
- This is no longer considered an associated effect of vancomycin therapy.

References

1. Bauer LA. *Applied Clinical Pharmacokinetics*. Chapter 5: Vancomycin. McGraw-Hill, 2001.

2. Rybak M, Lomaestro B, Rotschafer JC, Moellering R, Craig W, et.al. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Society of Infectious Diseases Pharmacists (SIDP). *Am J Health Syst Pharm*. 2009;66:82-98.

3. Brown M, Polisetty R, Gracely EJ, Cuhaci B, Schlecht HP. Weight based loading of vancomycin in patients on hemodialysis. *Clin Infect Dis* 2011;53(2):164-6.

4. Ariano, RE, Fine A, Sitar DS, Rexrode S, Zelenitsky SA. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. *Am J Kid Dis* 2005;46(4):681-7.

5. Panais R, Hirsch DJ, Dipchand C, Storsley L, Finkle SN. A protocolized approach to vancomycin dosing in conventional hemodialysis. *JNephrol* 2010;23(5):569-74.

6. Vandecasteele SJ, Bacquer DD, DeVriese AS. Implementation of dose calculator for vancomycin to achieve target trough levels of 15-20 mcg/mL in persons undergoing hemodialysis. *Clin Infect Dis* 2011;53:124-9.

7. Pai AB, Pai MP. Vancomycin dosing in high flux hemodialysis: a limited sampling algorithm. AJHP 2004;61:1812-6.

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VANCOMYCIN MONITORING: BEDSIDE APPROACH in ADULT PATIENT

PATIENT INFORMATION:
age, wt, ht, SCr, site of infection (will help determine targets), temperature, WBC (neuts), culture results, other medical conditions

IS THIS A NEW ORDER?

YES

IS SERUM CREATININE AVAILABLE?

NO

Get creatinine

Empiric dosing until creatinine available:

Dose: 15 mg/kg/dose based on actual body weight (max of 2 g/dose)

Interval: See dosing nomogram (Bugs & Drugs) or use
k_e= 0.00083*CrCl + 0.0044 to calculate $t_{1/2}$

YES

Calculate CrCl:

$$\text{CrCl (females)} = \frac{(140\text{-age}) \times \text{wt}}{\text{SCr } (\mu\text{mol/L})}$$

males = CrCl(female) x 1.2

See Bugs & Drugs for details on CrCl calculations

Calculate dose and interval:

1. Dose = 15 mg/kg based on actual body weight (max of 2 g/dose)
2. Interval:
   Use dosing guidelines as follows:

CrCl	Target 10-20 mg/L	Target 15-20 mg/L
≥ 80	Q12H	Q8H
40-80	Q24H	Q12H
20-40	Q36H	Q24H
10-20	Q48H	Q48H
< 10	Consider LD with levels**	

** See page 2 for further information on when to do levels and how to interpret them.

Trough Level:

1. Only if patient meets inclusion criteria
2. SCr at least once weekly (more if patient on concurrent nephrotoxic drugs, elderly, or renal function poor at baseline).

NO

DOES PATIENT MEET INCLUSION CRITERIA FOR TROUGH LEVEL MONITORING? (For criteria, see B*ugs &Drugs*)

YES

IS A TROUGH LEVEL AVAILABLE AND DRAWN APPROPRIATELY?

YES (IF "NO", ORDER TROUGH LEVEL AT STEADY STATE)

1. If patient is at steady state and level drawn appropriately determine if it is within target range.
2. If not within target, use ratio equation to determine degree of dosage adjustment required to move level into range:
   $$\frac{\text{Current dose/day}}{\text{Current trough}} = \frac{\text{New dose/day}}{\text{Desired trough}}$$
3. If patient is not within steady state, consider this when making recommendations on any dosage adjustment. i.e. if level has not risen to steady state value yet increasing the dose may overshoot your target. Likewise if level drawn on newly reduced dose, or in face of improving SCr, it may still be falling and you risk under-dosing if you overestimate the needed correction.

* Decision to leave dosage as is or check levels based on clinical assessment of case, including potential resistance of micro-organism

** See page 2 for further information on when to do levels and how to interpret them.

How to do a "pharmacokinetic consult":

1. Using calculated CrCl, estimate vancomycin ke using the following equation:
   Estimated ke = 0.00083 (CrCl) + 0.0044

2. Use est. ke to calculate other parameters as detailed in box to the right.

3. If dealing with a reported trough level that is unacceptably high, or low, order pre/post vancomycin levels within 24-48 hours, and follow the algorithm below:

Calculate dose and interval:

1. Identify desired Cmax and Cmin
   Use peak = 25 - 40 mg/L **(for calcs. only)**
   trough = 10 - 20 mg/L

2. Calculate dose:
   Dose = Vd x (Cmax –Cmin)
   (Vd(est) for vancomycin = 0.7 L/kg)

3. Calculate interval:
   Interval = 2 x $t_{1/2}$

4. Check Cmax
   $$Cmax = \frac{Dose}{(Vd \times (1 - e^{(-ke)(\tau)})}$$

5. Check Cmin
   $$Cmin = Cmax \times e^{(-ke)(\tau)}$$

Does patient meet criteria needed for pre and post vancomycin levels?

YES

ARRANGE TO HAVE PRE LEVEL DRAWN WITHIN ½ HOUR OF NEXT DOSE, AND POST LEVEL DRAWN AT LEAST 1 HOUR AFTER END OF INFUSION.

Calculate patient specific parameters, based on pre/post levels:

1. Calculate ke:
   $$ke = \frac{\ln(peak/trough)}{t}$$

2. Calculate half-life:
   $$t_{1/2} = \frac{0.693}{ke}$$

3. Calculate true peak:
   $$Cmax = peak \div e^{(-ke)(t_1)}$$

4. Calculate true trough:
   $$Cmin = trough \times e^{(-ke)(t_2)}$$

5. Calculate volume of distribution:
   $$Vd = \frac{Dose}{Cmax - Cmin}$$

NO

CONTINUE TO MONITOR USING TROUGH LEVELS ONLY..
CONTINUE TO MONITOR SCr AS RECOMMENDED.

CLINICAL PEARL:
Vancomycin exhibits linear kinetics so changes made in the dose will result in proportional changes in the level. E.g. If you have patient on 1 g q12h for a trough of 10 mg/L and you want 15 mg/L as a trough do the following:

$$\frac{2000 \text{ mg/d}}{10 \text{ mg/L}} = \frac{X \text{ mg/d}}{15 \text{ mg/L}}$$

X = 3000 mg/d or 1500 mg q12h (or 1000 mg q8h)

Multiple (2 posts or pre/post) vancomycin levels may be considered in situations where the level achieved with dosing adjustments is out of proportion to expectations. This may be due to the following reasons:

1. Patients with known, or suspected severely altered volumes of distribution (from population norms). e.g. neonates, critically ill, burns
2. Patients with known or suspected extremes of renal function. e.g. trough **much** lower than expected despite adjustments in dose

Important note: Even when doing pharmacokinetic calculations using multiple vancomycin levels, remember that the peak is not the focus of your calculations/recommendations, but only a step needed to determine the appropriate dose and interval.

KEY

ke - elimination rate constant
Cmax - actual peak level
Cmin - actual trough level
t - time difference between measured peak and trough (τ - ($time_{peak}$ - $time_{trough}$)
t_1 - time difference from end of infusion to measured peak level.
t_2 - time difference from measured trough level to start of infusion.
τ - interval

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