VANCOMYCIN - SCH

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Vancomycin is used in situations of suspected or proven antibiotic resistance or allergy, particular attention should be paid to its appropriate use and monitoring
- This guideline outlines the indications, dosing, and monitoring of intravenous vancomycin

CHANGE SUMMARY

- Minor changes to dosing for neonates.
- The time of measuring the trough level has been clarified.
- Dose adjustments based on Therapeutic drug monitoring: revised recommendations.
- Addition of continuous vancomycin infusions and TDM.
- Renal impairment: suggested doses revised.
- **May 2022**: Therapeutic drug monitoring now includes separate advice for invasive MRSA infections; ID consult recommended for continuous infusions and required for invasive MRSA infections.
- **Feb 2024**: Minor review. Corrected the initial trough levels to be taken prior to the fifth dose. See section 3.2

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st July 2021	**Review Period**: 3 years
Team Leader:	Staff Specialist	**Area/Dept**: Infectious Diseases

READ ACKNOWLEDGEMENT

The following staff are to read and acknowledge they understand the contents of this document:

- All staff at SCH who are involved in the provision of antimicrobial agents to SCH patients.
- Clinical Department Heads and Nursing Unit Managers at SCH.

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1 Background

Vancomycin, a glycopeptide antibiotic, is an essential antibiotic in the treatment of infections with certain Gram-positive microorganisms, particularly where there is suspected or proven antibiotic resistance. Glycopeptides are also an alternative class of antibiotics for use in patients allergic to beta-lactam antibiotics. Coagulase-negative staphylococci, enterococci and *Staphylococcus aureus* have all been reported to exhibit varying degrees of resistance to vancomycin.[1] In the interest of ensuring efficacy and limiting the spread of resistance, it is essential that appropriate and effective vancomycin treatment is used.

Vancomycin delivered as a continuous infusion increases the likelihood of maintaining a therapeutic steady state plasma concentration without increasing the risk of adverse events.[2,3] A continuous infusion may be considered if therapeutic drug levels are difficult to obtain using intermittent infusions or for those who are critically ill.

2 Indications

Vancomycin is appropriate or acceptable in the following situations[4,5]

- Treatment of serious infections due to beta-lactam-resistant Gram-positive microorganisms.

Clinicians should be aware that vancomycin is less effective than beta-lactam agents for beta-lactam-susceptible staphylococci and therefore vancomycin is ***not*** *recommended for therapy if a beta-lactam alternative exists.*

- Treatment of infections due to Gram-positive microorganisms in patients with serious hypersensitivity (IgE-mediated or non IgE-mediated delayed type) to beta-lactam antimicrobials and other antimicrobial agents are not available.
    - *Immediate hypersensitivity is characterised by the development of urticaria, angioedema, bronchospasm or anaphylaxis (with objectively demonstrated hypotension, hypoxia or elevated mast-cell tryptase concentration) within 1 to 2 hours of exposure to a drug.*
    - *Delayed reaction: characterised by macular, papular or morbilliform rash, occurring several days after starting treatment. Examples include serum sickness, DRESS syndrome and Steven-Johnson syndrome.*
- Indications for vancomycin use are available through the following resources:
    - Empiric Antibiotic Guideline-SCH
    - Guidance MS

3 Dosing for Intermittent Infusions

3.1 Neonates

Initial vancomycin maintenance dosages for neonates with normal renal function[4,6]

Postmenstrual age (NB1)	Postnatal age	Starting dose	Dosing frequency (NB2)	Timing of trough level (NB2)
<30^{+0} weeks postmenstrual age	0-2 days	15 mg/kg	18-hourly	Before the second dose (at 18 hours)
	3+ days	15 mg/kg	12-hourly	Before the third dose (at 24 hours) (NB3)
30^{+0}-36^{+6} weeks postmenstrual age	0-14 days	15 mg/kg	12-hourly	Before the third dose (at 24 hours)
	15+ days	15 mg/kg	8-hourly	Before the fourth dose (at 24 hours)
37^{+0}-44^{+6} weeks postmenstrual age	0-7 days	15 mg/kg	12-hourly	Before the third dose (at 24 hours)
	8+ days	15 mg/kg	8-hourly	Before the fourth dose (at 24 hours)

NB1: Postmenstrual age is the time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (postnatal age).

NB2: For neonates with impaired kidney function unrelated to age consult ID/Nephrology. If vancomycin is used perform trough before the second dose.

NB3: If postmenstrual age is less than 29^{+0} weeks obtain trough before the second dose

Critically ill neonates: Consider giving a loading dose of 20 mg/kg. Refer to the table above for timing of the next dose.

3.2 Infants and Children with normal renal function

Intermittent IV infusion: 15 mg/kg/dose 6-hourly to a maximum of 750 mg per dose

First trough should be taken prior to the fifth dose

NB1 For obese children with body mass index (BMI) for age and sex between the 95th and 99th percentiles, use actual (measured) bodyweight. Monitor for signs of nephrotoxicity. For children with a BMI for age and sex > 99th percentile, seek ID advice.[4]

For patients with GFR < 90 mL/min/1.73m^2 See: Patient with Renal Impairment or Risk Factors for Toxicity

Critically ill children: A loading dose of 25-30 mg/kg (actual body weight) up to 1500 mg can be considered in patients with severe sepsis. If a loading dose is given, it should be counted as the first dose.[4]

4 Preparation and Administration of Intermittent Infusions

Reconstitute vancomycin vials and further dilute with a compatible fluid to a concentration of no more than 5 mg/mL for peripheral administration. In fluid restricted patients a concentration of 10 mg/mL can be administered via central venous catheter.[7]

A 2 hour intermittent infusion is recommended to limit the risk of 'red-man' syndrome.[8] Patients with previous 'red-man' syndrome (see section 5.3) require longer infusion times (see Hypersensitivity reactions).

In patients receiving multiple IV medications, the infusion may be given over a shorter period but the rate of infusion must not exceed 10 mg/minute and the infusion must be given over at least 1 hour.[7]

Adequately flush the intravenous lines before and after administration.

Monitor for pain, redness and swelling at the insertion site throughout the infusion. Extravasation should be managed accordingly, see SCHN Extravasation Management.

5 Vancomycin Adverse Effects

5.1 Nephrotoxicity

- Risk of nephrotoxicity is increased with concomitant use of other nephrotoxic medications (e.g. aminoglycosides, amphotericin, cyclosporine, frusemide, vasopressors, non-steroidal anti-inflammatory drugs [NSAIDS]).[9-11]
- Acute kidney injury has been reported when piperacillin-tazobactam and vancomycin have been used concurrently. Renal function and hydration should be closely monitored.[12-14]
- Pre-existing renal impairment and obesity are also risk factors for nephrotoxicity.

5.2 Ototoxicity

- Although ototoxicity secondary to vancomycin is uncommon, vancomycin should be used with caution with concomitant ototoxic medications (e.g. aminoglycosides, frusemide, cisplatin).[7]

5.3 Hypersensitivity reactions

- The most common hypersensitivity reaction is an infusion-related anaphylaxis-like reaction, known as 'red-man' syndrome. This is characterised by flushing, erythema and pruritis, particularly of the upper body, head and neck. It is common and is related to the speed of infusion. The mechanism is direct mast cell activation by vancomycin. It is NOT a true, IgE-mediated allergy[4]. However, anaphylaxis to vancomycin can present with similar signs.
- Suggested management of 'red-man' syndrome:

- Stop the infusion.
- Assess for signs of anaphylaxis (i.e. urticaria, stridor, wheeze).
  - If these are present, manage as an anaphylactic reaction, including IM adrenaline. In these cases, vancomycin must be avoided in the future.
- If no signs of anaphylaxis are present, administer an antihistamine.
  - Once symptoms have subsided, the infusion can be re-started at one-half the original rate.
  - Future infusions of vancomycin should be administered over **four hours**. Consider pre-medicating with an antihistamine before infusions.
  - Document the reaction in the medical record.

6 Monitoring Vancomycin Intermittent Infusions

6.1 Renal Function

- All children prescribed vancomycin should have their renal function checked either prior to commencing therapy or at the time of their first serum level. Ongoing monitoring should consider timing of TDM and risk factors for nephrotoxicity.

6.2 Therapeutic Drug Monitoring

- Trough levels should be measured to ensure effective antimicrobial levels are reached. A higher serum concentration (indicated by the trough level) may be required for effective antimicrobial activity in bone, joint or central nervous system infections.
- Aim for a target trough level between **7-15 mg/L for children receiving 6-hourly vancomycin and neonates**.[15] Higher levels may be required for invasive MRSA infections – consult Infectious Diseases.
- The first serum level should be performed when “steady-state” is reached in all children with normal renal function (e.g., prior to the fifth dose of vancomycin when prescribed 6-hourly). A vancomycin trough level should be taken within 30 minutes before the next dose. See section 3.1 above for the timing of the trough level for neonates.
- In patients with normal renal function, **GIVE** the dose after taking the trough level. **DO NOT withhold** the next dose while awaiting the result as this usually results in the patient being under-dosed.
- If continuing therapy, subsequent trough levels should be performed in children with normal renal function:
  - 24 hours (or **prior to the fifth dose**) following a dose change.[4]
  - **every third day** if continuing therapy at the same dose and the patient is stable. Once two plasma concentration measurements (taken 24 to 48 hours apart) are in

the target range, monitor the vancomycin concentration at least weekly in stable patients.[4]

- More frequent TDM is required for hemodynamically unstable patients and should be considered when nephrotoxic medications are initiated or ceased.[16,17]
- To be able to interpret levels and adjust doses, the time the level is taken and the time the previous vancomycin dose was administered must be recorded.
- Falsely high levels can be obtained from samples taken from the same line that the drug was infused. Where available, obtain sample from a separate line or consider a finger prick sample.

6.3 Adjusting intermittent doses in children with normal renal function

The recommendations in this section assume the timing of the trough sample was appropriate (i.e., pre-dose) and steady state has been reached.

Trough level above the target range (7-15 mg/L)[15]

If the trough vancomycin level is greater than the target range and between 16-24 mg/L, the total daily dose should be decreased by 20%, while the dosing interval remained at 6-hourly. If the trough is >25 mg/L, check the patient's renal function and discuss with the Infectious Diseases team before giving further doses.

Trough level below the target range

If the vancomycin level is less than the target range, the total daily dose should be increased by 20%, while the dosing interval remains at 6-hourly. Recheck the level at 24 hours (or **prior to the fifth dose**) if the child remains on vancomycin. If the child has sepsis or CNS infection and the trough is still <7 mg/L despite dose adjustment, discuss with the Infectious Diseases team.

6.3.1 Adjusting intermittent doses in children with confirmed invasive MRSA infection and normal renal function

In recognition of a requirement for more aggressive therapy to treat invasive MRSA infections, vancomycin trough targets may be higher (e.g. 15-20 mg/L) and doses may be adjusted in a linear manner according to the steady state trough concentration for patients, after consulting with ID:

$$\textit{New daily dose} = \textit{previous daily dose} \; x \left(\frac{\textit{desired vancomycin level}}{\textit{measured vancomycin level}} \right)$$

The formula should **not** be used if:

- Trough concentration is far outside the therapeutic range or may not be reliable due to the timing of the sample or a missed dose
- Calculated total daily dose is ≥ 100 mg/kg/day or 4 g/day.[16] These doses are generally not required and should be avoided unless discussed with ID.

7 Vancomycin Continuous Infusion

Vancomycin delivered as a continuous infusion increases the likelihood of maintaining a therapeutic steady state plasma concentration without increasing the risk of adverse events.[2,3] A continuous infusion also permits more convenient monitoring of drug levels. It should only be considered after discussion with ID if therapeutic drug levels are difficult to obtain using intermittent infusions or for those who are critically ill.

Vancomycin is incompatible with other drugs commonly co-administered in the ICU. Independent lines or multiple catheters are required if vancomycin is administered as a continuous infusion.[16]

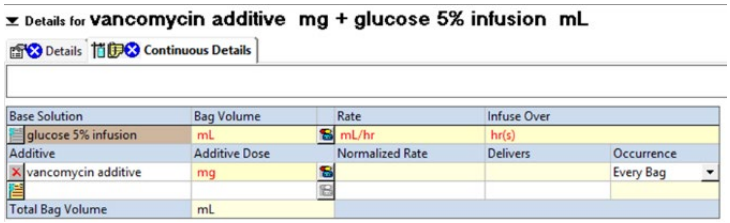
7.1 Prescribing Vancomycin Continuous Infusion

- **If commencing continuous infusion at outset of therapy**, give loading dose immediately followed by continuous infusion.

Dosing Guidance for initiating vancomycin as a continuous infusion			
Age and GFR (NB1)		**Loading dose**	**Continuous infusion dose**
Neonate	n/a	Refer to Australasian Neonatal Medicines Formulary: Vancomycin – continuous infusion regimen	
Infants and children 1 month and older	Normal renal function	15 mg/kg ONCE	60 mg/kg/day
	GFR<90 mL/min/1.73m^2	See Continuous infusion dosing in renal impairment	

NB1: GFR calculated using modified (bedside) Schwartz formula

- **If switching from intermittent dosing to continuous infusion**, commence the continuous infusion immediately following the last intermittent dose.
    - The starting dose for a 24-hour continuous infusion should be the sum of the intermittent doses of the preceding 24 hours. Dose adjustment may be needed if the trough plasma concentration with the intermittent regimen was far outside the target range – Consult ID
- The prescriber's order **must** specify:
    - Total daily dose of vancomycin,
    - Base solution (sodium chloride 0.9% or glucose 5%) and Bag Volume
        - maximum concentration: 5 mg/mL for peripheral OR 10 mg/mL for central lines. A more dilute solution is preferred.
    - **NB**, the Total Bag Volume in the eMM order will not be adjusted for each reconstituted vial of vancomycin that is added to the Bag. If required - add 20 mL for every 1 g of vancomycin that is added.
    - Infusion rate in mL/hr to deliver the total daily dose over 24 hrs.



7.2 Preparation and Administration of Vancomycin Continuous Infusion

Reconstitution of vials and dilution is the same as for intermittent infusions.

Continuous infusions should be administered over a 24-hour period with the total daily dose, base solution (sodium chloride 0.9% or glucose 5%), Total Bag Volume and infusion rate ordered by the prescriber on the continuous infusion section of the MAR.

- Any changes to the order should be made by the prescriber.
- The Total Bag Volume and rate MUST not altered by nursing staff.
- A new order and bag is required for dose adjustment.

7.3 Therapeutic Drug Level Monitoring of Vancomycin Continuous Infusion

- The target steady state plasma concentration range for vancomycin continuous infusions is 17-25 mg/L.
- Random vancomycin levels can be taken at any time from **24 hours after commencing the continuous infusion** – take as soon as is practical >24 hours.
- Specimens for vancomycin levels must be obtained peripherally and not from the same line as the infusion.
- If the vancomycin level is >25 mg/L, check renal function.
- If dose adjustment is required, repeat vancomycin level after at least 24 hours.

7.4 Dose adjustment for Vancomycin Continuous Infusion

Vancomycin continuous infusions demonstrate a linear relationship between the total daily dose (mg/day) and the corresponding steady state plasma concentration (mg/L). As such, adjustments to a new daily dose can be obtained by multiplying the previous daily dose by the desired vancomycin level divided by the measured vancomycin level.

$$\textit{New daily dose} = \textit{previous daily dose } x \left(\frac{\textit{desired vancomycin level}}{\textit{measured vancomycin level}}\right)$$

The table below provides a pragmatic dose adjustment calculation to achieve subsequent vancomycin levels within the target range of 17–25 mg/L.

Target level	Vancomycin Level	Dose Adjustment
17–25 mg/L	≤10 mg/L	Multiply dose by 2
	11–14 mg/L	Multiply dose by 1.5
	15–16 mg/L	Multiply dose by 1.2
	17–25 mg/L	No change
	26–29 mg/L	Multiply dose by 0.75
	≥30 mg/L	Stop infusion then recommence when level is <25 mg/L at half the previous dose

Doses 100 mg/kg/day or more are generally not required and should be avoided without prior discussion with ID.[16]

8 Patient with Renal Impairment or Risk Factors for Toxicity

Dosing and dose adjustment in patients with risk factors for toxicity, such as concurrent nephrotoxic drugs should be discussed with the Admitting Medical Officer.

Vancomycin excretion is influenced by glomerular filtration rate (GFR).

GFR can be estimated by the modified (bedside) Schwartz formula[18]:

$$\textbf{GFR} = \frac{\text{Height (cm)} \times 36.5}{\text{Serum creatinine (micromol/L)}}$$

- The dosing and interval of vancomycin depend on the estimated glomerular filtration rate.
- The following sections may be useful.

8.1 Intermittent dosing in renal impairment

Dosing guidance for intermittent dosing in renal impairment [18-20] [19-21]

GFR (NB1)	**Initial dose**	**Initial dose frequency**	**Timing of trough level**
50 - 90 mL/min/1.73m^2	15 mg/kg up to 750 mg	6-hourly	Before the second dose **WAIT** for the result before giving the next dose
30 - 50 mL/min/1.73m^2	15 mg/kg up to 750 mg	12-hourly	
10 - 29 mL/min/1.73m^2	15 mg/kg up to 750 mg	24-hourly	
<10 mL/min/1.73m^2	Seek advice		

NB1: GFR calculated using modified (bedside) Schwartz formula (above)

8.2 Continuous infusion dosing in renal impairment

Dosing Guidance for initiating continuous vancomycin in renal impairment

Age and GFR (NB1)		**Loading dose**	**Continuous infusion dose**
1 month and older:	GFR 50 – 90 mL/min/1.73m^2	15 mg/kg	60 mg/kg/day
	GFR 30 – 50 mL/min/1.73m^2	15 mg/kg	30 mg/kg/day
	GFR10 – 29 mL/min/1.73m^2	7.5 mg/kg	15 mg/kg/day
	GFR <10 or renal replacement therapy	Not recommended	

NB1: GFR calculated using modified (bedside) Schwartz formula (above)

8.3 Vancomycin Monitoring and Dose Adjustment in renal impairment

- In children with existing renal impairment or risk factors for toxicity, renal function and drug monitoring are essential to guide therapy. If vancomycin level is below or above the target level, please seek advice from the Department of Nephrology or Infectious Diseases
- Trough levels taken before the second intermittent dose do not reflect steady state concentrations and should be interpreted cautiously with advice from the Department of Nephrology or Infectious Diseases (ID).

9 References

1. Kucers A, Crowe SM, Grayson ML, Hoy JF. Vancomycin. The Use of Antibiotics, pp 763-90. Oxford: Butterworth-Neinemann, 1997
2. Hurst AL, Baumgartner C, MacBrayne CE, Child J. Experience with Continuous Infusion Vancomycin Dosing in a Large Pediatric Hospital. J Pediatric Infect Dis Soc 2019;8(2):174-9.
3. McKamy S, Chen T, Lee M, Ambrose PJ. Evaluation of a pediatric continuous-infusion vancomycin therapy guideline. Am J Health Syst Pharm 2012;69(23):2066-71.
4. Principles of Vancomycin Use [published 2019 Apr.Updated 2021 Aug]. In: eTG complete [digital]. Melbourne: Therapeutic Guidelines Limited; 2019 Apr. https://www.tg.org.au
5. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children. Clinical Infectious Diseases 2011;52(3):e18-e55.
6. Neonatal Medicines Formulary (NMF) Consensus Group. Newborn Care Centre Clinical resources – Medications. Neomed Formularies. [Internet] Sydney, NSW [cited 2021, May]; Available from: https://www.anmfonline.org/clinical-resources/
7. Stephanie Phelps TH, Kelley Lee , A . Thompson. Pediatric Injectable Drugs : The Teddy Bear Book - 11th ed. American Society of Health - System Pharmacists (ASHP); 2018.
8. Healy DP, Sahai JV, Fuller SH, Polk RE. Vancomycin-induced histamine release and "red man syndrome": comparison of 1- and 2-hour infusions. Antimicrob Agents Chemother 1990;34(4):550-4.
9. Fiorito TM, Luther MK, Dennehy PH, LaPlante KL, Matson KL. Nephrotoxicity With Vancomycin in the Pediatric Population: A Systematic Review and Meta-Analysis. Pediatr Infect Dis J 2018;37(7):654-61.

10. Feiten HDS, Okumura LM, Martinbiancho JK, Andreolio C, da Rocha TS, Antonacci Carvalho PR, et al. Vancomycin-associated Nephrotoxicity and Risk Factors in Critically Ill Children Without Preexisting Renal Injury. Pediatr Infect Dis J 2019;38(9):934-8.
11. Moffett BS, Morris J, Kam C, Galati M, Dutta A, Akcan-Arikan A. Vancomycin associated acute kidney injury in pediatric patients. PLoS One 2018;13(10):e0202439.
12. Downes KJ, Cowden C, Laskin BL, Huang YS, Gong W, Bryan M, et al. Association of Acute Kidney Injury With Concomitant Vancomycin and Piperacillin/Tazobactam Treatment Among Hospitalized Children. JAMA Pediatr 2017;171(12):e173219.
13. Hammond DA, Smith MN, Li C, Hayes SM, Lusardi K, Bookstaver PB. Systematic Review and Metaanalysis of Acute Kidney Injury Associated With Concomitant Vancomycin and Piperacillin/Tazobactam. Clinical Infectious Diseases 2017;64(5):666-74.
14. Bellos I, Karageorgiou V, Pergialiotis V, Perrea DN. Acute kidney injury following the concurrent administration of antipseudomonal β-lactams and vancomycin: a network meta-analysis. Clin Microbiol Infect 2020;26(6):696-705.
15. Frymoyer, A, Guglielmo, BJ, & Hersh, AL. (2013). Desired vancomycin trough serum concentration for treating invasive methicillin-resistant Staphylococcal infections. Pediatr Infect Dis J, 32(10), 1077-1079.
16. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2020;77(11):835-864.
17. Avedissian SN, Bradley E, Zhang D, Bradley JS, Nazer LH, Tran TM, et al. Augmented Renal Clearance Using Population-Based Pharmacokinetic Modeling in Critically Ill Pediatric Patients. Pediatr Crit Care Med 2017;18(9):e388-94.
18. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20(3):629-37.
19. Zhang H, Wang Y, Gao P, Hu J, Chen Y, Zhang L, et al. Pharmacokinetic Characteristics and Clinical Outcomes of Vancomycin in Young Children With Various Degrees of Renal Function. J Clin Pharmacol 2016;56(6):740-8.
20. Le J, Vaida F, Nguyen E, Adler-Shohet FC, Romanowski G, Kim J, et al. Population-Based Pharmacokinetic Modeling of Vancomycin in Children with Renal Insufficiency. J Pharmacol Clin Toxicol 2014;2(1):1017-26.
21. Aronoff GR, Bennett WM, Physicians ACo, Berns JS, Brier ME, Mueller BA, et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children. American College of Physicians; 2007.

Other references:

- Theresa S Cole, Andrew Riordan. Vancomycin dosing in children: what is the question? Arch Dis Child. 2013;98:994–997.
- Laura Broome and Tsz-Yin So. An Evaluation of Initial Vancomycin Dosing in Infants, Children, and Adolescents. International Journal of Pediatrics Volume 2011, Article ID 470364, 4 pages doi:10.1155/2011/470364
- de Hoog M, van Zanten BA, Hop WC, Overbosch E, Weisglas-Kuperus N, van den Anker JN. Newborn hearing screening: tobramycin and vancomycin are not risk factors for hearing loss. Journal of Pediatrics.142(1):41-6, 2003.