

Vancomycin Dosing and Monitoring in Adults Clinical Guideline

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**Government
of South Australia**

SA Health

Disclaimer

This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation. If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for:

- Discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary;
- Advising consumers of their choice and ensure informed consent is obtained;
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct; and
- Documenting all care in accordance with mandatory and local requirements.

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Vancomycin Dosing and Monitoring in Adults

1. Introduction

Vancomycin is a glycopeptide antibiotic. Intravenous formulations are used to treat infections with Gram-positive bacteria and for surgical prophylaxis in some situations.

The SA Medicines Formulary restricts use of intravenous vancomycin to the following indications in adults:

- > Infectious Diseases / Clinical Microbiology advice; or
- > Intensive Care Units; or
- > Haematology / Oncology as per febrile neutropenia guidelines; or
- > Surgical prophylaxis as per statewide clinical guidelines for patients allergic to penicillin or at high risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infection; or
- > Continuous Ambulatory Peritoneal Dialysis (CAPD) peritonitis involving MRSA and/or coagulase-negative staphylococcus (CoNS); or
- > Empiric treatment of sepsis for 48 hours only (continuing therapy only with ID / Microbiology advice).

2. Background

Therapeutic drug monitoring is recommended for all patients treated with vancomycin for longer than 48 hours to avoid under-dosing. Monitoring is also important to minimise the risk of toxicity, especially in patients with renal impairment (including those receiving renal replacement therapy).

Recent evidence has shown that the best determinant of vancomycin efficacy is the AUC/MIC [1]. A 24-hour AUC/MIC of 400 or more is the target for clinical success [2, 3]. For practical reasons, a trough (pre-dose) plasma concentration is used as a surrogate measure of efficacy.

3. Definitions and acronyms

ABW	Actual body weight
AUC/MIC	Ratio of area under the curve (plasma concentration vs time) to minimum inhibitory concentration (Units: mg.hr/Litre)
BMI	Body Mass Index = $(\text{Bodyweight in kilograms}) / (\text{height in meters})^2$
BSI	Blood stream infection/s
CAPD	Continuous ambulatory peritoneal dialysis
CNS	Central nervous system
CrCl	Creatinine Clearance
GFR	Glomerular filtration rate
ID/micro	Infectious diseases / Clinical microbiology

Low weight	Body weight < 50kg
MER	Medical Emergency Response
MET	Medical Emergency Team
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NSQHS	National Safety and Quality Health Service Standards
Obese	BMI > 30kg/m ²
PO	Orally
SAAGAR	South Australian SA expert Advisory Group on Antimicrobial Resistance
SBP	Systolic blood pressure
TDM	Therapeutic drug monitoring
Trough level	Serum vancomycin level taken towards the end of the dosing interval, approximately one hour prior to next dose

4. Loading dose

Based on the currently available evidence, clinical data support a loading dose of 25mg / kg (actual body weight) [3]. A loading dose will facilitate more rapid attainment of therapeutic target range [4]. Higher loading doses may be required for critically ill patients (e.g. meningitis, sepsis, burns) – consult ID/micro.

See [table 1 in the Appendix](#) for loading dose determination.

5. Maintenance dose and dose adjustments

Start maintenance dosing 12 hours after loading dose if CrCl more than/equal to 40mL/min, OR 24 hours after loading dose if CrCl = 20-39 mL/min. If CrCl is less than 20mL/min check trough level 24 hours after loading dose; wait for trough to fall below 20mg/L prior to re-dosing.

To estimate CrCl, use the Cockcroft-Gault equation (see table 5, Appendix). Do not use eGFR for dosing.

[Table 2 in the Appendix](#) presents suggested maintenance dosing for patients within the weight range between 40 & 120 kg, according to CrCl. Outside of this range, dosing based on actual body weight at 15 - 20 mg/kg per dose may be indicated (see under *Special Considerations* (Section 9) for information on dosing in obesity or low body weight). The doses in [Table 2 \(Appendix\)](#) are for initial dosing, up to 48 hours; Subsequent dosage adjustments for intermittent infusions should be according to recommendations in [Table 3 \(Appendix\)](#), and based on trough plasma concentrations.

6. Frequency of monitoring and dose adjustment

Therapeutic Drug Monitoring (TDM) is recommended for all patients treated with intravenous vancomycin for more than 48 hours to reduce the risk of under-dosing and minimise the risk of toxicity. The time of the first TDM (trough) will depend on the patient's renal function and/or if renal function is potentially unstable.

Trough monitoring

For patients with **normal renal function**, the first TDM (trough) should occur just prior (within one hour) to the **fourth** dose (including the loading dose) or on day 3, whichever occurs earlier. In patients with CrCl between 20-39 mL/min check trough level before (within one hour) of the **third** dose (including the loading dose). In changing renal function, earlier or more frequent TDM may be required. For patients with CrCl less than 20mL/min or on peritoneal dialysis check trough level 24 hours after **loading** dose. Repeat TDM trough (pre-dose) level every 3 days until levels are stable within the therapeutic range, and at least once weekly thereafter [5, 6]. Unless stated in the Appendix Table 3 (i.e. CrCl less than 20mL/min), doses should NOT be routinely withheld pending trough level result.

Renal function monitoring

Creatinine levels should be checked daily for the first 2 to 3 days of therapy, even if creatinine levels are in the normal range. Measure serum creatinine twice weekly. For patients with **unstable renal function** TDM should occur more frequently (possibly daily) to ensure toxicity is avoided.

7. Target therapeutic range

Target concentrations vary depending upon the disease, the MIC of the pathogen, and the mode of administration [7]:

- **Intermittent infusion:** Aim for trough levels of 15 - 20mg/L;
- **Continuous infusion:** Aim for blood levels of 20 - 25mg/L at steady state (36 – 48 hours after a dose change). See under '[Special considerations](#)' for further guidance on continuous infusions.

Due to its relatively large molecular weight, the penetration of vancomycin into the cerebrospinal fluid from the IV route is variable and dependent upon the degree of meningeal inflammation [8]. Depending upon the MIC of the pathogen, clinicians may aim for targets of 20 - 25mg/L to ensure sufficient CNS concentrations [9]– for further information seek advice from Infectious Diseases / Clinical Microbiology/ Clinical Pharmacist.

8. Administration

Doses of 1g should be administered over at least 60 minutes [10]. For higher doses the duration of infusion should be extended by 30 minutes for each additional 500mg. This is recommended to reduce the risk of 'red man syndrome' [11]. The usual dilution is 5mg/mL. For fluid-restricted patients, concentrations of up to 10mg/mL may be used.

Minimum recommended infusion durations are shown in [Table 4 \(Appendix\)](#), adapted from Wilson & Estes (eds), 2011 [12].

9. Special Considerations

Continuous infusions

Continuous infusion of vancomycin may be preferable in patients where the target range is difficult to achieve via intermittent infusion, and may be necessary to maintain adequate blood levels in patients with augmented renal function or obese patients [13]. It is currently unclear whether administering vancomycin via continuous infusion is associated with less nephrotoxicity than intermittent infusions, as the key correlating factor appears to be the steady-state vancomycin concentration [7, 14].

Switching from intermittent dosing to continuous infusion: For patients initiated on intermittent dosing and then switching to continuous infusion, the starting dose over 24 hours is the same as the total dose for 24 hours administered via intermittent infusion [3]. The continuous infusion should be started immediately after the last intermittent dose. For patients being discharged and continuing treatment at home, and with levels in the upper end of the target range (e.g. 20mg/L), local experts from SAAGAR recommend a dose reduction of approximately 20% when converting from intermittent to 24-hour continuous infusion.

Initiating vancomycin with continuous infusion: For critically ill patients initiated on continuous infusion (and not initially treated with intermittent infusion), an initial loading dose is recommended (Table 1, Appendix). If the patient is not critically ill, the initial dose is the same as an intermittent maintenance dose (Table 2, Appendix). Continuous infusion is to be commenced immediately after the completion of the loading dose – a level is not required at this point. The subsequent 24-hour continuous infusion is the sum of the intermittent doses that would have been given over a 24 hour period, according to the patient's CrCl [9].

For patients with normal renal function, steady-state concentration is reached after 36-48 hours. During continuous infusions blood concentrations may be measured at any time of the day once steady-state is achieved [15, 16]. In unstable patients, true steady state may never be achieved [16]. Levels may be done earlier (e.g. 16 hours after infusion initiated) in critically ill patients to enable early identification of sub-therapeutic levels. Dosage adjustments are made in a simple linear manner [3]. Levels should be monitored every 2-3 days, or more frequently if renal function is unstable, for example, in the ICU setting.

Red man syndrome

Red man syndrome is a common non-immunological reaction that can occur during or shortly after an infusion of vancomycin and is related to the *rate* of infusion. For this reason, it is recommended that vancomycin is infused no faster than 1g/hour [11]. The reaction is mediated by histamine release, which can result in pruritus, flushing, erythematous rash (face, neck and upper thorax predominantly), fever, chills and in severe cases angioedema and hypotension. These symptoms are due to non-specific mast cell degranulation. True IgE-mediated allergy can occur but is rare.

If a patient experiences an infusion related reaction to vancomycin:

- > Cease infusion
- > Administer antihistamine (cetirizine 10mg PO)
- > If newly hypotensive (SBP less than 90mmHg) initiate a call requesting emergency medical assistance (i.e. MET or MER call). Consider giving adrenaline (epinephrine) if unable to do so.

- > Consult clinical pharmacist or infectious diseases team for advice on recommencement of vancomycin at a **slower rate** of infusion. Local experts from SA recommend doubling the time to infuse the solution, or changing to a continuous infusion.

Dosing in obesity

Obese patients are at higher risk of insufficient vancomycin concentrations leading to poorer clinical outcomes [17]. The volume of distribution is larger in the obese population, protein binding may be altered and clearance of vancomycin may also be greater.

Morbidly obese patients are excluded from most clinical trials therefore the evidence to guide dosing regimens in these patients is not strong [4].

Based on current clinical practice, the initial loading dose in obese patients should be as for non-obese patients, using actual body weight (at 25mg/kg), (maximum 3 grams loading dose if CrCl is more than or equal to 60mL/min or 2.5g if CrCl is less than 60mL/min) [3]. More frequent dosing (8-hourly) or a continuous infusion may be preferred in obese patients [18]. Higher doses of more than 4g per day, such as those often required in obese patients, are associated with a higher risk of nephrotoxicity [19, 20].

Recommended maintenance dosing in obese adults is variable due to the differing pharmacokinetics secondary to the extent of obesity and any pre-existing renal impairment, and should be guided by TDM.

Low body weight <50kg

Consider 15-20mg/kg 12-hourly maintenance dosing for patients less than 50kg, appropriately adjusting the dose if the patient also has impaired renal function. Loading doses less than 25mg/kg and less frequent dosing may be appropriate in these patients [21]. Ongoing dosing should be guided by TDM.

Haemodialysis

Vancomycin dosing in adults undergoing intermittent haemodialysis is challenging due to a prolonged distribution phase, a redistribution phase and rebound effect after completion of haemodialysis, patient weight and residual renal function, and non-renal clearance [22]. Dialysis frequency also affects maintenance dosing [23]. Loading doses are independent of renal function and should be based on actual body weight (see table 1 in the Appendix). In most situations, levels should be done at the beginning of each haemodialysis session to guide further dosing. If levels are done post-dialysis, allow at least four hours after the end of dialysis to allow for tissue redistribution [22].









Continuous renal replacement therapies (CRRT)

Vancomycin is effectively cleared by continuous renal replacement therapies, however the clearance may be impacted by the type of CRRT chosen: continuous veno-venous haemofiltration (CVVH), continuous veno-venous haemodialysis (CVVHD) and continuous veno-venous haemodiafiltration (CVVHDF) [24]. Clearance is closely related to the rate of ultrafiltrate / dialysate flow. Loading doses based on ABW should be used in patients receiving CRRT (Table 1, Appendix). In fluid overloaded patients, doses may require reduction as the volume of distribution is decreased [23]. In general, administration of vancomycin by continuous infusion is preferred in patients on CRRT. Maintenance dosing should be based on serum concentration monitoring [23].

10. Safety, quality and risk management

This guideline is in accordance with the following National Safety and Quality Health Service Standards (NSQHSS):

National Safety and Quality Health Service Standards

 National Standard 1 Clinical Governance	 National Standard 2 Partnering with Consumers	 National Standard 3 Preventing & Controlling Healthcare-Associated Infection	 National Standard 4 Medication Safety	 National Standard 5 Comprehensive Care	 National Standard 6 Communicating for Safety	 National Standard 7 Blood Management	 National Standard 8 Recognising & Responding to Acute Deterioration
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Standard 1.7: Set out, review and maintain the currency and effectiveness of, policies, procedures and protocols;

Standard 3.15: Provides access to, and promotes the use of, current evidence-based Australian therapeutic guidelines and resources on antimicrobial prescribing;

Standard 4.13 The health service organisation ensures that information and decision support tools for medicines are available to clinicians.

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11. Document Ownership & History

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30/12/2019	V1.1	Director, Communicable Disease Control Branch	Minor alteration and put in the new template.
06/12/2016	V1.0	SA Health Safety & Quality Strategic Governance Committee	Original approved version.

Table 1: Vancomycin loading dose determination

Actual body weight (kg)	Loading dose (grams)
40-44kg	1g
45-54kg	1.25g
55-64kg	1.5g
65-79kg	2g
80-119kg or more than/equal to 120kg & CrCl less than 59ml/min	2.5g
More than/ equal to 120kg and CrCl more than/ equal to 60ml/min	3g* (maximum)

* High loading doses recommended based on expert advice and current practice in Australia and evidence of safety [25-27]

Table 2: Recommended initial maintenance dose (for up to 48 hours)

Creatinine clearance (mL/min)*				
Actual body weight (ABW) See ID/micro advice if Less than 40kg	Start maintenance dose 12 hours after loading dose (if giving 12-hourly) or 24 hours after the loading dose (if giving 24 hourly)			Check level 24 hours after loading dose. *Re-dose only when level is less than 20mg/L. Repeat levels every 1-2 days
	CrCl more than 60	CrCl 40-59	CrCl 20-39	CrCl less than 20 or CAPD
40 – 49 kg	750mg 12-hourly	750mg 12-hourly	750mg 24-hourly	750mg [#]
50 – 64 kg	1g 12-hourly	750mg 12-hourly	1g 24-hourly	1g [#]
65 – 78 kg	1.25g 12-hourly	1g 12-hourly	1.25g 24-hourly	1.25g [#]
79 – 92 kg	1.5g 12-hourly	1.25g 12-hourly	1.5g 24-hourly	1.5g [#]
93 – 107 kg	1.75g 12-hourly	1.25g 12-hourly	1.75g 24-hourly	1.75g [#]
More than 108 kg	2g 12-hourly	1.5g 12-hourly	2g 24-hourly	2g [#]

*Use the Cockcroft-Gault equation (Appendix 2) to calculate CrCl. Do not use eGFR as this is not accurate for extremes of body size.

Table 3: Dosage adjustment for intermittent infusions based on trough concentration

Creatinine clearance (mL/min)				
		CrCl more than 40 mL/min	CrCl 20-39	CrCl less than 20
Timing of vancomycin level:		Check level before the fourth dose (incl loading dose)	Check level before the third dose (incl loading dose)	Check level 24 hours after loading dose*
Trough concentration	Less than 10 mg/L	Increase <u>total daily dose</u> by 1g (Seek ID advice if daily dose more than 4g/day)	Increase <u>total daily dose</u> by 500mg	Re-dose when trough less than 20mg/L
	10 – 14 mg/L	Increase total daily dose by 500mg	Increase <u>total daily dose</u> by 250mg	
	15 – 20 mg/L	IN TARGET RANGE - no change required. Repeat trough levels twice weekly if vancomycin levels and renal function are stable. If not, more frequent monitoring is suggested*		
	21 – 25 mg/L	Reduce each dose by 250mg		
	More than 25mg/L	Hold dose for 24 hours. Re-check level and recommence at reduced dose when level Less than 20mg/L. Review renal function		

* Wait for result from lab before re-dosing, then re-dose according to doses recommended in Table 2. Dosing frequency is usually 48-72 hrlly

Additional dosing information:

- As a general rule, round doses to the nearest 250mg; Vial sizes available are 500mg or 1g.
- Following a dose adjustment, vancomycin levels and serum creatinine should be ordered 36-48 hours after the new dose was started.
- Doses of up to 1g should be administered over at least 60 minutes to avoid 'red man syndrome'. For higher doses, the duration of infusion should be extended by 30 minutes for each additional 500mg.
- For continuous infusions, aim for steady state (after 36 to 48 hours) levels of 20-25mg/L or as advised by ID/micro.

Table 4: Intravenous infusion rate

Vancomycin Infusion Rate	
Dose	Recommended Infusion Duration
Less than / equal to 1 g	60 min
1.1 - 1.5 g	90 min
1.6 - 2.0 g	120 min
More than 2 g	Infuse at approx. 1 g per hour

Table 5: Estimating CrCl using the Cockcroft-Gault equation

Ideal body weight estimation:

Feet & inches	Cm	IBW (female)	IBW (male)
5'1	155	48	53
5'2	157	50	55
5'3	160	53	57
5'4	163	55	60
5'5	165	57	62
5'6	168	60	64
5'7	170	62	66
5'8	173	64	69
5'9	175	66	71
5'10	178	69	73
5'11	180	71	76
6'0	183	73	78
6'1	185	76	80

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{IBW (kg)} \times 0.85 \text{ (for females)}}{720}$$

$$0.815 \times \text{SeCr (micromol/L)}$$

*Use Actual Body Weight if this is LESS than IBW

- If obese (ABW is $\geq 30\%$ above IBW or BMI $> 30\text{kg/m}^2$), consider using adjusted body weight (AdjBW) to calculate CrCl:

$$\text{AdjBW} = \text{IBW} + [0.4 \times (\text{ABW} - \text{IBW})]$$

IBW (female) = 45.5kg + 0.9kg per cm over 152cm

IBW (male) = 50kg + 0.9kg per cm over 152cm

For more information

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