Vancomycin Continuous Infusion in Critically Ill Adults Clinical Guideline

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Contents

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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).

The utilisation of continuous infusions in critically ill patients aims to align the pharmacokinetics and pharmacodynamics of vancomycin and is currently recommended in international guidelines.

Note: Recommendations on the administration of vancomycin continuous infusions **outside of the critical care setting** are not within the scope of this guideline. Please refer to SA Health Vancomycin Dosing and Monitoring in Adults Clinical Guideline.

2. Background

In the critically ill patient, alterations in pharmacokinetics increase the risk for failure to meet pharmacokinetic targets to ensure efficacy.[1] With antimicrobials in septic patients, the need for rapid attainment of these targets correlates directly with mortality.[2]

The utilisation of continuous infusions of vancomycin has been shown to more rapidly reach therapeutic concentration and has been associated with lower rates of nephrotoxicity when compared to intermittent dosing.[3]

3. Definitions

AUC	Area Under the Curve
CAPD	Continuous Ambulatory Peritoneal Dialysis
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CNS	Central Nervous System
CoNS	Coagulase Negative Staphylococcus
CrCl	Creatinine Clearance

CRRT	Continuous Renal Replacement Therapy
CVVHF	Continuous Veno-Venous Haemofiltration
ECMO	Extracorporeal Oxygenation Membrane
EDD	Extended Daily Dialysis
eGFR	Estimated Glomerular Filtration Rate
ICU	Intensive Care Unit
IgG	Immunoglobulin G
MET	Medical Emergency Team
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
PO	Orally
TDM	Therapeutic Drug Monitoring

4. Loading Dose

International guidelines currently recommend that all critically ill patients receive a loading dose of vancomycin prior to initiation of therapy. In order to rapidly attain therapeutic concentrations a loading dose of 20-35 mg/kg, based on actual body weight is recommended. Current recommendations suggest capping loading doses at 3000 mg.[4]

See Table 1 in appendix for loading dose determination.

If the patient has been receiving vancomycin therapy prior to admission to the Intensive Care Unit, they should be converted to a continuous infusion. A loading dose may be required depending on their serum vancomycin concentration on admission to the ICU – See Table 2 in appendix for conversion to the continuous infusion.

5. Maintenance Dose and Dose Adjustments

Following completion of loading dose, the vancomycin continuous infusion should be commenced immediately as per Table 3 in appendix.

Where possible an estimation of renal function should be undertaken using a 24-hour measured urinary creatinine clearance, however in practice calculating an estimation using the Cockcroft-Gault equation can act as a surrogate.[1] In critically ill patients, laboratory reported eGFR (SA Pathology utilise the CKD-EPI formula) should not be used when assessing renal function for routine drug dosing, however it has been identified as a useful tool in identifying patients with Augmented Renal Clearance.[1 5]

6. Target Therapeutic Range

Due to the pharmacodynamic target of vancomycin, a higher target concentration is required for continuous infusions. This is in order to maximise area under the curve (AUC), which is reduced due to the lack of peak concentrations.

- **Target concentration 20-25 mg/L at steady state** [4]

Vancomycin is considered to have a moderate level of CNS diffusion [6], as such, a higher target concentration may be required for CNS infections. Additionally, pathogens with a higher vancomycin MIC may require a higher target concentration, for further advice regarding these pathogens an infectious diseases / clinical microbiology team should be consulted.

7. Frequency of Monitoring and Dose Adjustments

Therapeutic drug monitoring (TDM) is recommended for all patients receiving intravenous vancomycin. For ***intermittent*** dosing, the recommended time of first serum vancomycin concentration is prior to the fourth dose. Due to the pharmacokinetic profile of a continuous infusion, trough concentrations are not achieved. Sampled concentrations should be referred to as steady state concentrations.

A steady state concentration should be sampled no sooner than 16 hours [2] following the initiation of the continuous infusion. Given the pharmacokinetic flux that septic and critically ill patients exist in, time to steady state varies widely. In order to ensure prompt bactericidal concentrations are achieved a level at 16 hours, if not at a steady state yet, will likely be close to steady state enabling clinicians to adjust infusion rate as required.

Following initial sampling, daily TDM should be undertaken until two consecutive consistent concentrations are obtained, at which point sampling should be taken every 48 hours unless further concentration fluctuations occur.

Patient deterioration or the initiation/withdrawal of extracorporeal clearance or supports (e.g. Continuous Renal Replacement Therapy (CRRT) or Extracorporeal Oxygenation Membrane (ECMO)) should necessitate more vigilant TDM as these may affect the clearance and serum concentration. Pre-emptive dose adjustments should be considered at the cessation of renal replacement therapy, in particular if there is suspicion of reduced renal function in the patient.

In order to reduce the risk of error and vancomycin infusion reaction (previously known as ‘Red Man Syndrome’) the rate rather than the concentration of the vancomycin should be altered to make dose adjustments when required. Given the general linearity of vancomycin’s pharmacokinetics dose adjustments can be calculated using a simple formula:

New rate = current rate x (22.5 ÷ most recent level)
Round answer up to nearest 0.5 mL/hour

Example of rate adjustment calculation
Current rate = 5 mL/hour Most recent level = 14 mg/L
New rate = 5 x (22.5 ÷ 14) = 5 x 1.6 = 8.03 mL/hour
New rate = 8.5 mL/hour

In the instance of a significantly supratherapeutic concentration (greater than 30.1 mg/L):

1. Ensure that concentration has been sampled appropriately (e.g., not taken immediately following loading dose or sampled from the same line the infusion is running through).
2. Review renal function.
3. Hold infusion for 6 hours and recheck level.
4. Once concentration has returned to therapeutic range (below 25 mg/L), adjust dosage as above (based on the infusion rate that resulted in the supratherapeutic concentration). If the new rate is below 3.8 mL/hour consider intermittent dosing as outlined in Table 4.
5. Continue to monitor concentrations daily as outlined above.

8. Administration

Patients receiving continuous infusions of vancomycin should receive a set concentration (1000mg/120mL), any dose changes should be made via a rate adjustment as opposed to a concentration adjustment.

Loading doses should be infused over the period of time as outlined in Table 1.

The use of continuous infusions of vancomycin outside of the ICU should be avoided, unless the patient is under the direct care of an Infectious Diseases / Clinical Microbiology team.

Infusion Compatibility

Continuous vancomycin infusions are compatible with peripheral administration. It is recommended that the peripheral cannula be placed in the cubital fossa or above, as opposed to the metacarpal vessels, but this is not a contraindication if unable to be placed elsewhere. Regular checks of infusion sites must be undertaken to ensure extravasation, erythema and signs of phlebitis have not occurred, as vancomycin is a known irritant.

Vancomycin is able to be run concurrently through the same lumen as a number of common ICU infusions. See Table 4 for some common ICU infusions. For further information regarding compatibility please contact an ICU clinical pharmacist.

Alteration of the concentration of the vancomycin continuous infusion may affect the physical compatibility with other drugs and should be avoided.

Vancomycin Infusion Reaction (previously known as 'Red Man Syndrome')

Note: Previous vancomycin infusion reaction DOES NOT preclude future vancomycin use

If a severe reaction was experienced previously, an immunology consult is required prior to initiation.

Vancomycin infusion reaction is a non-immunological reaction which can occur during or shortly after an infusion of vancomycin, which is related to the rate of infusion. 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. If a patient experiences an infusion related reaction to vancomycin consult clinical pharmacist or Infectious Diseases team for advice on recommencement of vancomycin at a slower rate of infusion.

True IgE-mediated allergy can occur but is rare. Therefore, correct documentation of adverse reactions is essential in guiding future treatment with vancomycin.

The term "red man syndrome" has historically been used to describe the histamine-mediated non-immunological reaction as described above. Recent evidence has implicated this terminology with gender and race-related bias, which can lead to incorrect identification and under-documentation of this adverse reaction.[7] In a cross-sectional study of EMR records for 4,490,618 patients, reactions representing this syndrome were more likely to be documented for males than females (OR, 1.30; 95% CI, 1.17 to 1.44) and less likely for darker-skinned patients than white-skinned patients (OR, 0.59; 95% CI, 0.47 to 0.75).[7]

Incomplete or incorrect documentation can lead to the avoidance of vancomycin in the future or to the use of less appropriate alternative agents. Replacing the term "red man syndrome" with "vancomycin infusion reaction" reduces the risk of gender or racial bias associated with the syndrome, thereby improving the diagnosis and documentation of adverse reactions.

9. Special Considerations

Extremes of Body Weight

Data regarding the dosing of vancomycin in both extremes of body weight (obesity and low) in critically ill patients is limited. Regardless of body size, these patients should have more frequent TDM undertaken, in particular in the early phase of vancomycin therapy.

Obese patients should receive a loading dose (20-25 mg/kg) based on actual body weight capped at 3000 mg [4 8], subsequent dosing should be based upon the patient's creatinine clearance and TDM.

There are significant limitations in evidence regarding dosing recommendations in low body weight patients. These patients should receive a loading dose as per Table 1. Judgement should be applied with respect to intensity of loading dose depending upon patient's clinical status. Subsequent dosing should be based upon the creatinine clearance and TDM, keeping in mind that these patients may have falsely low serum creatinine levels due to reduced muscle mass and that a measured urinary creatinine clearance may be required.

Intermittent Haemodialysis

Due to fluctuations in clearance in patients undergoing intermittent haemodialysis, vancomycin administered via continuous infusion is not recommended. Instead patients should have post dialysis serum concentrations sampled, and intermittent stat doses of 1 g if concentrations are below 15 mg/L. See Table 5 for dosing recommendations.

Continuous Renal Replacement Therapy

The different modalities of Continuous Renal Replacement Therapy (CRRT) will all clear vancomycin efficiently to varying degrees. See Table 5 for dosing recommendations.

Following initiation of CRRT, due to changes in volume of distribution and clearance, previously stable steady state concentrations will become in flux. As such serum concentration levels should be drawn at 16 hours following the initiation of CRRT. If the patient has an acute kidney injury prior to the initiation of CRRT, a rate increase should be considered as clearance of vancomycin will likely increase once CRRT starts.

Following cessation of CRRT, there will be a phase of redistribution and altered clearance. Typically clearance will reduce, in particular if the patient has an ongoing kidney injury, as such serum concentration levels should be drawn at 16 hours following the cessation of CRRT. A pre-emptive rate reduction on the cessation of CRRT is also recommended to prevent supratherapeutic levels from occurring.

10. Transition to ward therapy

Due to the complexity of the administration of continuous infusions of vancomycin, and the ease of intermittent dosing, when a patient is transferred out of the ICU they should be transferred to intermittent dosing.

Dose conversion is outlined in Table 6.

In order to maintain therapeutic concentrations, the first intermittent dose should be given immediately following the cessation of the continuous vancomycin infusion. This should be considered time zero for subsequent ongoing dosing.

A vancomycin serum concentration should be sampled immediately prior to the third intermittent dose, with further dose adjustments as per the SA Health Vancomycin Dosing and Monitoring in Adults Clinical Guideline.

11. Appendices

Table 1: Loading Dose - Initial Therapy

Actual Body Weight (kg)	Loading Dose (grams)
40-44kg	1g
45-54kg	1.25g
55-64kg	1.5g
65-79kg	2g
80-119kg	2.5g
>120kg and CrCl <59ml/min	2.5g
>120kg and CrCl ≥60ml/min	3g (maximum)

Table 2: Loading Dose - Conversion to Continuous Infusion from Intermittent

Vancomycin Level	Required Loading Dose
<10mg/L	Loading dose of 25mg/kg
10-19.9mg/L	Loading dose of 10mg/kg
20-25mg/L	***Loading dose NOT required -*** commence infusion as per Table 3
>25mg/L	Contact ICU clinical pharmacist for advice

Table 3: Initial Continuous Infusion Dosing

Creatinine Clearance	Infusion Rate	Total Dose Over 24 hours*
<10mL/min	See Table 5	
10-20mL/min	3.8mL/hour	750mg
21-30mL/min	5 mL/hour	1000mg
31-45mL/min	6.3 mL/hour	1250mg
46-60mL/min	7.5 mL/hour	1500mg
61-84mL/min	8.8 mL/hour	1750mg
85-95mL/min	10 mL/hour	2000mg
96-110mL/min	11.3 mL/hour	2250mg
111-130mL/min	12.5 mL/hour	2500mg
131-180mL/min	13.8 mL/hour	2750mg
≥181mL/min	15 mL/hour	3000mg

*Dose rounded to nearest 50mg

Table 4: Common ICU Drug Infusion Compatibility with Vancomycin

Compatible		Incompatible
Adrenaline	Ketamine	Aminophylline
Amiodarone	Labetalol	Flucloxacillin
Anidulafungin	Magnesium Sulphate	Frusemide
Argatroban	Meropenem	Heparin
Azithromycin	Metronidazole	Methylprednisolone Sodium Succinate
Ciprofloxacin	Midazolam	Moxifloxacin
Clindamycin	Milrinone	Pantoprazole
Dexmedetomidine	Morphine	Phenytoin
Dobutamine	N-Acetyl-Cystine (NAC)	Piperacillin/Tazobactam (Tazocin)
Dopamine	Potassium Chloride	Propofol
Fentanyl	Remifentanil	Sodium Valproate
Insulin	Vasopressin	Trimethoprim/Sulfamethoxazole

Table 5: Dosing in Renal Impairment or Renal Replacement Therapy

CrCl ≤ 10mL/min	Give 25mg/kg loading dose as per above then take daily levels. When vancomycin levels drop below 15mg/L administer 1g stat dose
EDD	Give 25mg/kg loading dose as per above then take post dialysis as well as routine daily levels. When vancomycin levels drop below 15mg/L administer 1g stat dose
CVVHF (2L exchange)*	Give 25mg/kg loading dose as per above and commence at 6.3mL/hour (~1200mg/24 hours) Take daily levels and adjust rate as recommended
CVVHF (4L exchange)*	Give 25mg/kg loading dose as per above and commence at 10mL/hour (~2000mg/24 hours) Take daily levels and adjust rate as recommended
ECMO	Give 25mg/kg loading dose as per above and commence continuous infusion as per Table 3, or as above if on CVVHF Take daily levels and adjust rate as recommended

*Ensure dose is adjusted when CVVHF is ceased

Table 6: Conversion to Ward Therapy

Infusion Rate	Dose Conversion for Ward
<2.5mL/hour	Stat 1g dosage when serum vancomycin concentration <15mg/L
2.6-3.5mL/hour	1000mg daily
3.6-6mL/hour	750mg 12 hourly
6.1-8.5mL/hour	1000mg 12 hourly
8.6-11mL/hour	1250mg 12 hourly
11.1-13.5mL/hour	1000mg 8 hourly
13.6-16mL/hour	1250mg 8 hourly
16.1-19mL/hour	1000mg 6 hourly
>19mL/hour	Contact ICU clinical pharmacy service

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13. Document Ownership

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