Ballarat Health Services

DRUG GUIDELINE

Vancomycin (Adult patients)

SCOPE (Area): **FOR USE IN:** All ward areas, except as outlined below
EXCLUSIONS: Paediatrics (seek Paediatrician advice)
SCOPE (Staff): Medical, Nursing and Pharmacy

BRAND NAMES
No brand names.

PHARMACOLOGY, PHARMACOKINETICS & MICROBIOLOGICAL SPECTRUM

Vancomycin is a glycopeptide antibiotic that appears to act by inhibiting the production of bacterial cell wall mucopeptide. This effect occurs at a site different from that affected by penicillins and produces immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane. There is also evidence that vancomycin alters the permeability of the cell membrane and selectively inhibits RNA synthesis

Vancomycin is primarily eliminated via renal excretion of unchanged drug (80-90%) via glomerular filtration. Its rate of elimination is related to creatinine clearance and there is no apparent metabolism of the drug. Normal elimination half-life in adults is 5-11 hours (200-250 hours in end-stage renal disease). The volume of distribution of vancomycin is 0.4-1L/kg.

Vancomycin is effective against a wide range of Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant coagulase negative staphylococcal species (e.g. *Staphylococcus epidermidis*). Vancomycin may be used in severe infections in patients hypersensitive to penicillin and in meningitis due to highly penicillin-resistant *Streptococcus pneumonia.*

Due to the emergence of vancomycin-resistant enterococcus (VRE) and glycopeptide intermediate *Staphylococcus aureus*, parenteral vancomycin should be used only when there is strong suspicion of infection with MRSA, MRSE or other serious gram positive organisms where alternative agents are unsuitable.

INDICATIONS

- Treatment of suspected or confirmed serious Gram-positive infections as per microbiological spectrum listed above.
- Empiric treatment as part of the BHS Adult Sepsis Pathway.
- As an alternative antibiotic for patients with a suspected or documented beta-lactam allergy, guided by the current version of Therapeutic Guidelines: Antibiotic.
- Treatment of *C. difficile* diarrhoea (severe cases), or patients who have experienced multiple relapses of disease (oral vancomycin).

CONTRAINDICATIONS

Allergy to vancomycin

PRECAUTIONS

Allergy to teicoplanin (cross sensitivity may occur)
Renal impairment – adjust dose (see below)
Patients with previous severe hearing loss
Oral administration: inflammatory bowel conditions may allow significant oral vancomycin absorption, especially in renal impairment.

PREGNANCY AND BREASTFEEDING

Seek specialist advice before prescribing, information may update regularly. See Breastfeeding And Medications: CPG0088

DRUG INTERACTIONS

Vancomycin can cause nephrotoxicity and ototoxicity; administration with other oto- or nephrotoxic drugs can add to these adverse effects (eg. aminoglycosides, amphotericin B, cyclosporin, loop diuretics).

Increased rates of nephrotoxicity have recently been reported from retrospective and uncontrolled prospective studies when vancomycin is co-administered with piperacillin/tazobactam, however there is no high-quality randomized controlled trial evidence of this interaction, and the basis or possible mechanism of this interaction is not understood.

DOSAGE AND ADMINISTRATION

Vancomycin may be administered via the following methods. See each method for detailed information

1. INTERMITTENT INTRAVENOUS ADMINISTRATION

Loading doses: **are required to rapidly achieve therapeutic levels and should be followed by consistent intermittent dosing. Loading dose is independent of renal function, however maintenance doses are prescribed at intervals depending on renal function.** Consideration should be given to previous vancomycin doses (if applicable) that achieved therapeutic concentrations. It may be appropriate to initiate vancomycin maintenance dosing at the previously tolerated dose in these patients (providing renal function is stable)

Maintenance doses: the doses recommended in the subsequent tables are a guide to achieve adequate therapeutic levels. Patients with severe sepsis who fall close to the edge of two intervals (ie. either bodyweight or renal function) and require aggressive therapy should be given the higher dose or greater frequency.

Renal dosing adjustment: **vancomycin dosing in renal replacement therapy is complicated, and differs depending on the method of renal replacement therapy.** Consult ID/pharmacy for advice regarding dosing or dose adjustments for patients receiving renal replacement therapy. **See appendix 1 for recommended dosing regimens and monitoring requirements.**

Dosing in obesity: Vancomycin dosing in obese patients is complex. For patients with a BMI up to 35kg/m^2, use actual body weight. For patients with a BMI greater than 35kg/m^2, seek ID or pharmacy advice, especially for septic patients or those with renal impairment. In such patients, early therapeutic drug monitoring (TDM) (in some cases prior to the second dose) is recommended to allow prompt recognition of sub- or supra-therapeutic levels and to guide ongoing dosing.

Intermittent intravenous administration of vancomycin in adults

Round all doses to the nearest 250mg increment

STEP 1 – Loading dose

25-30mg/kg (25mg/kg if well, 30mg/kg in sepsis)

Dose according to **actual body weight**
Use lower range for dosing for low bodyweight patients
Discuss morbidly obese patients with ID or pharmacy (or doses greater than 3g)
Maximum infusion rate 10mg/minute

STEP 2 – Maintenance dose

15-20mg/kg

Dose according to **actual body weight**
Calculate Creatinine Clearance (CrCl) to determine frequency. The use of eGFR is not appropriate for calculating drug doses

Vancomycin Maintenance Regimen	Creatinine clearance mL/min (as estimated by Cockcroft Gault equation) (Creatinine Clearance Calculator)		
	Less than 20mL/min	20 to 60mL/min	Greater than 60 mL/min
	Use lower end of dosing range		
Dosing Frequency	48-72 hourly	24 hourly (daily)	12 hourly (twice daily)
Trough level due: (loading dose considered first dose)	48 hours after first dose *	Before 3rd dose	Before 4th dose
* Discuss dosing regimen with pharmacy/ID. Re-dosing is only appropriate when trough levels less than or equal to 20mg/L			

Step 3 – Monitoring and subsequent maintenance dosing

Target trough level: 15 to 20mg/L (refer to monitoring section)

- Therapeutic drug monitoring should be started before the 4th dose in patients with normal renal function, or sooner in the case of renal impairment (see Step 2 for recommended trough level timing).
- Levels should be considered earlier if a significant change in renal function occurs.
- Adjust subsequent doses according to trough level (by adjusting dose or frequency, but not both).
- Do NOT withhold dose while awaiting level result (unless advised by ID/pharmacy, or CrCl less than 20).
- Consider 8 hourly dosing in patients with low levels on standard dosing regimens, or those requiring greater than 4g per day. Discuss with ID/pharmacy.

- **Exposure to trough levels less than 10mg/L has been associated with the development of resistant organisms.**

- Aim to transition to a continuous infusion as soon as patient identified as candidate for HITH. Infusions are as effective as intermittent dosing and associated with reduced toxicity.

Intermittent intravenous administration: Dose adjustment in adults

Higher or lower trough concentrations than targeted require adjustment of dosage interval and/or dose. Changes in dose without changes in interval will result in proportional changes in trough concentration provided renal function remains stable. It is recommended that dose adjustments be done in a simple linear fashion.

For example, if target concentration is 15mg/L but measured trough level is only 10mg/L for a dose of 1g, the dose has to be adjusted by a factor of 15/10, or 1.5 fold, therefore the new dose will be 1.5g. Dose adjustment should be made to the nearest 0.25g.

Trough level (mg/L)	Suggested daily vancomycin dosage adjustment
Less than 10*	**Increase by ~50%. A "mini" loading dose may need to be considered in these patients. Discuss with ID or Pharmacy.**
10-15	**Increase by ~25%**
15-20	**No change**
20-25	**Decrease by ~25% (unless target is up to 25mg/L for CNS infections)**
25-30	**Decrease by ~50%**
Greater than 30	**Withhold next dose. Do not administer next dose until level less than 20mg/L. Refer to ID/pharmacy for advice**

* There is an increased risk of resistance when trough levels are less than 10mg/L. Ensure that subsequent dosage is increased according to this guideline.

To confirm appropriate dosage and frequency following a dose change, a second trough level should be taken 48 hours later.

Unexpected high or low blood concentration levels should be repeated to rule out blood collection or pathology error.

Blood samples should be taken via peripheral venepuncture.

Although the use of lower troughs (10-14mg/L) has been suggested for some patients (version 16 of the Therapeutic Guidelines: Antibiotic), this is NOT appropriate unless the minimum inhibitory concentration of the organism is known, and AUC monitoring is being used. The use of trough levels less than 15 as a therapeutic target MUST be discussed with ID.

2. Vancomycin dosing for continuous intravenous infusion.

Continuous infusions of vancomycin are commonly used in a Hospital in the Home setting, and can be considered for patients requiring large intermittent doses of vancomycin (for example, patients with good renal function and a large body weight).

Continuing inpatient therapy following intermittent dosing:

The starting 24 hour infusion dose should be 80-100% of the total intermittent infusion for the preceding 24 hours if levels, dose and renal function were stable. From clinical experience, a reduction in dosage by up to 20% results in the most effective treatment. Speak to ID or AMS pharmacist for further advice.

Aim to transition to a 24 hour infusion as soon as it is decided to treat a patient under HITH, and trough levels are stable.

Infusions of 24 hour duration can be commenced at any time regardless of the time of administration of the last intermittent dosage.

Commencing a continuous intravenous infusion: no prior vancomycin therapy

All patients not previously receiving intermittent infusions of vancomycin **MUST** receive a loading dose. Failure to give a loading dose prior to commencing a continuous infusion will result in a prolonged period of sub-therapeutic levels of up to 3 days.

Prescribe vancomycin loading dose as indicated (25-30mg/kg based on actual body weight). Calculate the 24 hour dose based on doses recommended in the Maintenance dose table for intermittent infusions.

The 24 hour infusion is started as soon as the loading dose is complete.

It is uncommon to require more than 4g over 24 hours. Doses above 4g should be discussed with ID or pharmacy.

Dose adjustment for continuous infusions

Recommended target concentrations for continuous vancomycin infusion is 17-25mg/L.

Steady-state trough level	**Dose adjustment for CrCl greater than 50mL/min * #**
Less than 17mg/L	Increase total dose. Consider a "stat" dose of vancomycin depending on level (discuss with ID/AMS)
17-25mg/L	No dose change required
25-27mg/mL	Reduce dose of next scheduled infusion. Consider stopping the current infusion for 12-24 hours (dependant on age and renal function. Discuss with ID/AMS)
Greater than 27mg/L	Exclude collection error. Stop infusion until levels less than 25mg/L and Reduce total dose of next scheduled infusion.

In general, a single dose increase should not be more than 50% of the daily dose
*For patients with a CrCl less than 50mL/min, consideration should be given to using intermittent infusions.

Dose adjustment should be done in a linear fashion, as outlined in intermittent intravenous dosing section.

Unexpected high or low blood concentration levels should be repeated to rule out blood collection error.

Blood samples should be taken via peripheral venepuncture.

3. Oral vancomycin dosing (for *Clostridium difficile* diarrhoea)

Oral vancomycin is restricted to use for severe disease or subsequent disease recurrence.

The recommended dose is 125mg orally 6 hourly for 10 days, although higher doses up to 500mg orally 6 hourly may be used under the direction of ID.

ID should be contacted if oral vancomycin is being considered.

Note:

- Intravenous vancomycin is ineffective for the treatment of *Clostridium difficile* due to poor penetration into the colon
- Vancomycin blood levels and dosage adjustment in renal impairment is not required for oral dosing as it generally doesn't penetrate the mucosa, however a spot level could be considered for patients with severe renal impairment and inflammatory bowel conditions to ensure doses are not accumulating significantly.
- Vancomycin solution for oral dosing is supplied by BHS pharmacy. If required outside of pharmacy hours, solution for oral administration can be prepared using an IV vial by nursing staff: Reconstitute vial to a concentration of 50mg/mL with water for injection as per AIDH. Withdraw dosage and administer orally or via enteral feeding tube. Flavouring syrup or orange juice may be added to improve palatability. Remaining solution can be stored for up to 96 hours in the refrigerator. Solutions kept in the refrigerator must be clearly labelled with 3 patient identifiers, an enteral label (as per CPP0222 User Applied Labelling of Injectable Medicines, Fluids and Lines) and the date reconstituted.
- Oral capsules are only considered for use in Outpatients or on discharge due to significantly higher cost.

General Administration Information

Timely administration of vancomycin is essential to ensure serum levels can be accurately interpreted, and that vancomycin levels remain therapeutic. Following a loading dose, the next dose should be commenced after the number of hours prescribed for the maintenance dose have elapsed.

For example, if a patient was prescribed a 2.5g loading dose, commenced at 6am, and then a 1.5g 12 hourly maintenance dose, the first 1.5g maintenance dose would be commenced at 6pm, that is 12 hours after the loading dose was STARTED.

- **Infusion preparation:** Refer to Australian Injectable Drugs Handbook in each clinical area

    - Dilute concentration to less than 5mg/mL. A concentration of less than 10mg/mL may be used in fluid restricted patients.

For fluid restricted patients in ICU with CVC access see DRG0048 Antibiotic and Electrolyte Maximum Concentrations for Fluid Restricted patients

- **Volume to be removed from IV bag:** Nil.
- **Infusion Rate:** **Wards:** Maximum rate 10mg/minute

Haemodialysis administration: Maximum rate 25mg/minute during high-flux dialysis

- **Infusion pump:** Alaris LVP with Guardrails
- **Routes of administration:**
  - IV injection: Not recommended.
  - IV intermittent infusion: Yes
  - IV continuous infusion: Yes
  - IM injection: Contraindicated. Causes ulceration and necrosis
  - Subcut injection: No.
- **Compatible/incompatible IV drugs/fluids:**
  Consult the Australian Injectable Drugs Handbook ('Yellow book') in your ward area. **Assume all unlisted drugs and IV fluids are incompatible – contact Pharmacy for further advice.**

MONITORING (INCLUDING BLOOD TESTS).

Recommended target levels:

- **Intermittent infusion:** 15-20mg/L. Higher levels, eg. 20 – 25mg/L for CNS infections may occasionally be required under the direction of ID/microbiology.
- **Continuous infusion:** 17-25mg/L at steady state.

Commence therapeutic drug monitoring at a time suitable according to patients renal function. See Maintenance dosing table for guidance on when to commence therapeutic drug monitoring:

- Trough levels are taken 30 minutes prior to administering a dose.
- Document time of sample collection on the pathology request slip.
- **Administration of the next due vancomycin dose should not be delayed or withheld whilst awaiting trough level results** UNLESS specifically advised by the treating doctor or clinical pharmacist. Subsequent vancomycin doses will be adjusted accordingly if out-of-range trough levels are detected.

To confirm appropriate dosage and frequency following a dose change, a second trough level should be taken 48 hours later.

Stable patients on prolonged vancomycin treatment should have trough concentrations and renal function monitored twice weekly, but more frequently if patients have impaired or rapidly changing renal function, or are receiving concomitant nephrotoxins (e.g. aminoglycosides, loop diuretics).

High vancomycin levels (greater than 30mg/L) may require the next dose to be withheld until the patient can clear the previous dosage. Discuss with ID/pharmacy. Ensure that the sample has been taken at the correct time, and has not been taken through a central line.

Unexpected high or low trough levels should be repeated to rule out blood collection or pathology error. Confirm that the timing of the trough level was correct and consider whether steady state concentration has been reached (e.g. if patient's renal function is changing rapidly).

NURSING PRACTICE POINTS

Vancomycin is an irritant and may cause local inflammation and rarely cause necrosis if extravasation occurs.

For small amounts of extravasated drug causing minor symptoms:

- Apply a COLD compress. Leave in place for 15-20 minutes. Can be repeated up to four times per day for 48 hours if necessary.
- Mark any demarcated area with an indelible pen. If there is any deterioration in the injury, the surgical team should be contacted.
- Enter a RiskMan (VHIMS) incident

ADVERSE EFFECTS

"Red man" syndrome:

- Is an infusion reaction (NOT an allergy) and may manifest as flushing or rash of the upper body and neck, muscle spasm of the chest and back, and rarely, hypotension and shock-like symptoms during the vancomycin infusion. To prevent recurrence:
  - Slow the rate of infusion
  - Pre-medicate with anti-histamines

If these measures do not help, use of teicoplanin may be considered (must be discussed with ID).
Document incidence of Red man syndrome in patient history.

Thrombophlebitis
Nephrotoxicity (defined as an increase in serum creatinine of ~45 micromol/L or ≥50% increase from baseline, whichever is greater) Nephrotoxicity due to vancomycin is usually reversible on cessation of therapy.
Ototoxicity (dizziness, vertigo, and tinnitus). Vancomycin alone rarely causes ototoxicity
Neutropenia (following prolonged therapy).
Thrombocytopenia
Extravasation (see nursing practice points for treatment)

DRUG PRESENTATIONS AND STORAGE

Vancomycin 500mg and 1g vials
Store at room temperature.

RELATED DOCUMENTS

SOP0001 Clinical Care
POL0083 Antibiotic Policy
CPP0262 Antimicrobial Stewardship
CPP0635 Adult Sepsis Pathway
CPP0222 User Applied Labelling of Injectable Medicines, Fluids and Lines
DRG0048 Antibiotic and Electrolyte Maximum Concentrations for Fluid Restricted patients

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APPENDIX 1

Vancomycin dosing in renal replacement therapy

	Continuous renal replacement eg. CVVHDF[1]	Haemodialysis[2, 3]	Peritoneal Dialysis-Peritonitis
Loading dose	25 to 30mg/kg (Actual body weight. Use 30mg/kg dose in sepsis)		Refer to Melbourne Health "Treatment of Peritonitis in CAPD" guideline
Maintenance dose	1g 12-hourly* Experience at BHS suggests that during CVVHDF, initial doses of 1g 12-hourly will generally produce serum levels of 20-25mg/L. Adjust dose based on subsequent serum levels (consider residual renal function effect on clearance) *Speak to ICU or AMS pharmacist	15-20mg/kg (actual body weight)	
Frequency of dosing	12-hourly (unless otherwise determined by levels)	Determined by levels Re-dose when: • Pre-dialysis level less than 25mg/L • Non-dialysis day level less than 20mg/L	
Trough level due (post initial loading dose)	Daily (Consider taking first level 12 hours post-loading dose)	Daily Dialysis days: pre-dialysis level taken each run Mark pathology request as urgent and do not administer next dose until result is available	
Administration time	During dialysis	During dialysis. Conclude infusion at the same time as dialysis	

1. If CVVHDF is ceased and vancomycin treatment must continue, plasma concentrations of vancomycin should be determined 4-6 hours after stopping CVVHDF before re-dosing. Discuss with ICU/AMS pharmacist.
2. High flux haemodialysis: up to 20-46% of the vancomycin dose can be extracted by high flux membranes. This increases with dialysis duration. Low flux membranes remove vancomycin poorly.
3. Avoid taking a level within 6 hours post dialysis conclusion, as this is the distribution phase of the drug and erroneous levels may be returned.

Unexpected high or low trough levels should be repeated to rule out blood collection or pathology error. Consider withholding next dose if trough level is high.