the children's hospital at Westmead

VANCOMYCIN DOSING - CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- **Starting dose:** 15 mg/kg/dose 6 hourly for patients 4 weeks – 12 years of age with normal renal function. Maximum initial dose is 3 g/day.
- **Initial trough level monitoring** - at least 24 hours after the first dose
- **DO NOT** withhold the next dose while awaiting the result of the trough in patients with normal renal function
- **Therapeutic trough level range** - 10 to 20 mg/L. A level of 15 to 20 mg/L is recommended in complicated infections.
- **Seek expert advice** regarding dosing and monitoring in patients with impaired renal function
- For additional information: CHW Drug Dosage Guidelines at: http://chw.schn.health.nsw.gov.au/o/apps/picu/drug_doses/
- For further information: Page 6658 (Senior Pharmacist, Antimicrobial Stewardship), your ward pharmacist, or the Medical Microbiologist on-call

CHANGE SUMMARY

- Updated recommendations for continuous infusion guidelines
- Modified recommended dose adjustments for target level attainment

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st March 2016	**Review Period**: 3 years
Team Leader:	Pharmacist	**Area/Dept**: Antimicrobial Stewardship – CHW

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READ ACKNOWLEDGEMENT

- Medical officers, Pharmacists and Nursing staff who prescribe or administer vancomycin are to read and acknowledge they understand the contents of this document.

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This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

1 Background [1]

Vancomycin is a glycopeptide antibiotic that has activity against most Gram positive organisms and is often used against serious Staphylococcal infections (including MRSA) when treatment with other antibiotics has failed or the strain has been shown to be resistant.

Staphylococcus aureus is a bacterium that can live harmlessly on the skin and in the nose. It may cause infections on broken skin or wounds, osteomyelitis or septicaemia.

Glycopeptide - slowly bactericidal

- Glycopeptides are less effective than beta-lactams (such as flucloxacillin and cephazolin) at killing beta-lactam susceptible organisms such as methicillin-sensitive *Staphylococcus aureus* (MSSA) [2-4].
- The best determinant of vancomycin efficacy is the ratio of the area under the concentration–time curve to the minimum inhibitory concentration (AUC:MIC)[5]. However for practicality, measurement of the trough plasma concentration is recommended as a surrogate measure of efficacy.
- Under-dosing in *Staphylococcus aureus* is associated with the development of low level vancomycin hetero-resistance, and subsequent treatment failure.

It is important to reach the therapeutic serum levels as quickly as possible, both for maximal efficacy and to prevent the emergence of resistance.

2 Dosing

- Vancomycin is dosed according to ACTUAL BODY WEIGHT [6, 7].

Starting Intravenous (IV) Dose (normal renal function):

Neonate:

	Age	Weight	IV Dose	Frequency
Pre-term [8]	≤ 7 days	≤1500 g	20 mg/kg	24 hourly
		>1500 g	15 mg/kg	12 hourly
	> 7 days	≤1500 g	10 mg/kg	8 hourly
		>1500 g	15 mg/kg	8 hourly
Term [9, 10]	≤ 7 days		15mg/kg	12 hourly
	> 7 days		15mg/kg	8 hourly

Infants and Children[1]:

Age	IV Dose	Frequency	Maximum starting dose
Infants and children*	15 mg/kg	6 hourly	3 g/day
>12 years	30 mg/kg	12 hourly	

***N.B.** Loading doses of **30 mg/kg/dose** may be given for serious infections (sepsis, meningitis, pneumonia and endocarditis) for **infants and children**. This is based on expert opinion of more rapid attainment of target concentrations.[1, 11]
(E.g. 30 mg/kg/dose loading **THEN AFTER 6 HOURS** give 15 mg/kg/dose every 6 hours.)

Dose Adjustment for renal impairment in infants and children [12]:

- The following dose adjustments have been recommended based on the patients glomerular filtration rate (GFR).
- The following recommendations are based on a usual dose of 60 mg/kg/day rather than 40 mg/kg/day. This supersedes the PICU dialysis drugs dosing 2005 guideline.
- GFR can be estimated by the Schwartz formula:

GFR (mL/min/1.73 m^2) = (36.5 × Height in cm) / Creatinine in micromol/L

GFR (mL/min/1.73 m^2)	IV Dose	Frequency
50 - 30	15 mg/kg/dose	12 hourly
29 - 10	15 mg/kg/dose	24 hourly
< 10	10-15 mg/kg/dose	Re-dose based on levels (usually every 4-7 days)
Intermittent haemodialysis		
Peritoneal dialysis		
Continuous renal replacement therapy	15 mg/kg/dose	Re-dose based on levels (usually every 12-24 hours)

3 Preparation and Administration for Intermittent Infusion

	Intermittent Infusion [10, 13]
Preparation	<u>For 500 mg vial:</u> Reconstitute 500 mg vial with 10 mL Water for injection
	<u>For 1000 mg vial:</u> Reconstitute 1000 mg vial with 20 mL Water for injection
Dilute	Dilute to 5 mg/mL with either Normal Saline 0.9% or Dextrose 5% if being administered via Peripheral line. (For administration via Central Line only – can be diluted to 10 mg/mL) **<u>More dilute concentrations are preferred.</u>**
Rate	Infuse intravenously at a rate of 10 mg/min or a minimum of 1 hour (whichever is longer) ***For example:*** ***250 mg over at least 1 hour*** ***500 mg over at least 1 hour*** ***750 mg over at least 1.5 hours***

- If the infusion rate is too rapid, this can cause a histamine-mediated effect, which is generally referred to as "red man syndrome", involving a red rash over the upper body.
- This is **NOT** a true drug allergy and should not prevent further vancomycin administration - *Please speak to a Microbiologist for further advice*. If a rate related infusion reaction occurs, note the rate at which the infusion was running. Any further doses should be administered at a slower rate for that patient and use more dilute concentrations. Document the reaction in the notes or on the chart.

4 Therapeutic Drug Monitoring

A trough level MUST be performed at least 24hrs after the first dose.	
12 hourly dosing	immediately before the 3rd or 4th dose
8 hourly dosing	immediately before the 4th or 5th dose
6 hourly dosing.	immediately before the 5th or 6th dose

The half-life of vancomycin is approximately 4 to 6 hours and plasma levels are available 24 hours a day.

In patients without renal impairment, **DO NOT withhold the next dose** while awaiting the result of the trough level – this usually results in the patient being under dosed.

Target trough concentration [1]	
Uncomplicated infections:	10 to 20 mg/L
Complicated infections*: *(e.g. Bacteraemia, endocarditis, osteomyelitis, meningitis, necrotising fasciitis and pneumonia)*	15 to 20 mg/L

**Higher trough concentrations are recommended to optimize vancomycin pharmacodynamics, improve tissue penetration, and minimize selection of resistant strains*

- Vancomycin is renally cleared – monitoring of plasma urea and creatinine concentrations is important in the prevention of toxic vancomycin trough levels.
- Vancomycin levels should be monitored **weekly**
- More frequent vancomycin levels will be required if patient has renal impairment OR on other nephrotoxins (e.g. aminoglycosides, NSAIDs or amphotericin B)
- Dose adjustments should be done in a linear manner (see table on next page)

Recommended subsequent dose adjustments for INTERMITTENT infusion target attainment:

Target Trough	Trough Concentration	Dose Adjustment
10 to 20 mg/L	<5 mg/L	↑ 50%
	6 – 8 mg/L	↑ 30%
	8 – 10 mg/L	↑ 10%
	10 – 20 mg/L	No change
	20 – 25 mg/L	↓ 20%
	25 – 30 mg/L	↓ 30%
	30 – 40 mg/L	↓ 50%
	> 40 mg/L	Withhold one dose and decrease subsequent doses by 50%
After dose adjustment, repeat levels after 24 hours		

If vancomycin levels are high, monitor renal function closely, if renal function has declined, increase dosing interval according to patient's GFR as per table on page 4.

5 Monitoring Renal Function

- Urea and creatinine should be measured at commencement then at least twice weekly while on vancomycin.

6 Dosing and Monitoring in Patients with Renal Impairment

- In patients with impaired renal function, expert advice regarding dosing should be sought from your ward pharmacist, the Senior Pharmacist – Antimicrobial Stewardship (page 6658), or the Medical Microbiologist on-call.
- Therapeutic Drug Monitoring is required more frequently than in patients with normal renal function, and in advanced renal impairment it may be appropriate to withhold the next dose while awaiting the results of the drug level.

7 Adverse Effects

- Anaphylactoid reactions including hypotension, palpitations, substernal pressure, tachycardia, wheezing, dyspnoea, urticaria, or pruritus. This reaction may be rate related and the rate of infusion should be noted and decreased.
- Histamine-mediated effect ("red man syndrome") involves a rash over the upper body and is associated with too rapid an infusion rate and peak serum levels (this is NOT a true allergy, and should not prevent future use if it is indicated). Note the rate of infusion at the time of the reaction and decrease the infusion rate for any future doses. Document in the notes or on the chart.
- Ototoxicity (< 2% of patients) associated with persistently elevated trough levels
- Nephrotoxicity (rare, and associated with persistently elevated trough levels)
- Reversible haematological abnormalities (neutropenia, eosinophilia, thrombocytopenia)
- Systemic hypersensitivity reactions including nephritis, rash, hepatitis etc.

8 Vancomycin continuous IV infusion [14-18]

Converting from intermittent dosing to a continuous infusion is recommended if therapeutic targets are not achieved after 3 unsuccessful dose adjustments

- Vancomycin exhibits time dependent killing, which implies that maintaining trough serum concentrations above the MIC is the most important determinant of therapeutic outcome.
- Vancomycin given as a continuous infusion avoids high peak concentrations and allows the maintenance of a steady state concentration above the MIC.

- Additional benefits of a vancomycin continuous infusion include:
  - Less nursing time required for administration
  - Random vancomycin levels can be obtained for therapeutic drug monitoring
  - Less cost of acquisition and wastage

9 Dosing guideline for continuous IV infusion

Age:		24 hour IV dose	Loading dose*
Pre-term		Not recommended	
Term	<1 week	30 mg/kg	15 mg/kg
	1 week – 1 month	45 mg/kg	22.5 mg/kg
>1 month	GFR > 50	60 mg/kg	30 mg/kg
	GFR 50 – 30	30 mg/kg	15 mg/kg
	GFR 29 – 10	15 mg/kg	7.5 mg/kg
	GFR <10 or PD/HD/CRRT	Not recommended	

When to start the continuous infusion:

- If switching from an intermittent to continuous infusion, the continuous infusion should be commenced IMMEDIATELY after completion of the last intermittent dose infusion (NO loading dose required).
- *If starting initially with a continuous infusion, a loading dose should be given first and the continuous infusion commenced immediately after the end of the loading dose infusion.

10 Preparation and Administration for Continuous Infusion[13]

	Continuous Infusion
Preparation	Reconstitute vials as for intermittent infusion
Dilute	Dilute to 5 mg/mL with either Normal Saline 0.9% or dextrose 5% (can dilute to 10 mg/mL for administration via Central Line only) **More dilute concentrations are preferred**
Administration	Infuse over 24 hours
Stability	24 hours at room temperature

11 Therapeutic Range for Continuous Infusion [14, 18, 19]

Target concentration
20 – 25 mg/L

- Higher target concentrations are recommended due to smaller peak concentrations and less fluctuations over the dosage interval
- Random levels can be taken for therapeutic drug monitoring of continuous infusions
- **Levels can be taken 24 hours after starting the continuous infusion**
- Dose adjustments should be done in a linear way (see table below)
- If vancomycin level is high, monitor creatinine level if one has not been ordered within the last 24 hours

Recommended subsequent dose adjustments for CONTINUOUS infusion target attainment:

Target level	Drug Concentration	Dose Adjustment
20-25 mg/L	≤10 mg/L	Double dose
	11 – 13 mg/L	↑ 75%
	14 – 15 mg/L	↑ 50%
	16 – 17 mg/L	↑ 25%
	18 – 19 mg/L	↑ 15%
	20 – 25 mg/L	No change
	26 – 29 mg/L	↓ 15%
	30 – 34 mg/L	↓ 30%
	35 – 39 mg/L	↓ 40%
	> 40 mg/L	Stop infusion for 6 – 12 hours then recommence at 50% daily dose reduction
After dose adjustment, repeat levels after 24 hours		

For further information

- Please contact the Antimicrobial Stewardship consultant on pager 7092.
- The Infectious Diseases Fellow on pager 6675 or the Antimicrobial Stewardship Pharmacist on pager 6658
- After hours or on weekends, contact the Microbiologist on-call via switchboard.

12 References

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