the children's hospital at Westmead

VANCOMYCIN DOSING - CHW

PRACTICE GUIDELINE ©

KEY POINTS

- **Starting dose:** 15 mg/kg/dose 6 hourly for patients 4 weeks to 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
- **Therapeutic trough level range** - 10 to 20 mg/L. A level of 15 to 20 mg/L is recommended in severe infections.
- **Seek expert advice** regarding dosing and monitoring in patients with impaired renal function
- For further information: Page 6658 (Senior Pharmacist, Antimicrobial Stewardship), your ward pharmacist, or the Medical Microbiologist on-call

CHANGE SUMMARY

- Modified recommended dose adjustments for target level attainment
- Updated recommendations for continuous infusion guidelines
- Steady state target level for continuous infusion changed to 17 - 25 mg/L
- Therapeutic drug monitoring service now available
- Updated dosing in renal impairment for neonates.

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.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st September 2018	**Review Period**: 3 years
Team Leader:	Pharmacist	**Area/Dept**: Antimicrobial Stewardship – CHW

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1 Background[1-5]

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 and the strain has been shown to be sensitive to vancomycin.

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, endocarditis 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).
- The best determinant of vancomycin efficacy is the ratio of the Area Under the Concentration–time curve to the Minimum Inhibitory Concentration (AUC:MIC). However for practicality, measurement of the trough plasma concentration is recommended as a surrogate measure of efficacy. The target AUC is 400 mg.h/L and is preferred in patients with complicated pharmacokinetics or severe MRSA infections.[17]

CHW Therapeutic Drug Monitoring service:

Please page the AMS pharmacist during working hours #6658 to calculate the AUC.

- 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

Vancomycin pharmacokinetics in paediatrics:

- The clearance of vancomycin is faster in children compared to adults; neonates have a much slower clearance due to the underdeveloped renal function[9].

Age group	Half-life (hours)
Neonate	6 to 10
3 months – 18 years	2.2 to 4
Adult	4 to 6

Dosage forms available at CHW:

- 500 mg vials for injection
- 1 gram vials for injection

Continuous 24 hour infusors may be ordered for Hospital in the Home (HITH), please contact Infectious Diseases for approval and the HITH Department to be admitted.

24-48 hours is required for the order to be made by the Pharmacy Department.

2 Dosing[6-10]

- Vancomycin is dosed according to ACTUAL BODY WEIGHT.

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

Newborns (as per Neomed guideline):

	Postmenstrual Age	Postnatal Age	IV Dose	Frequency
Pre-term	< 30 weeks	0—2 days	15 mg/kg	18 hourly
	< 30 weeks	>3 days	15 mg/kg	12 hourly
	30 —36 weeks	0—14 days	15 mg/kg	12 hourly
	30 —36 weeks	>14 days	15 mg/kg	8 hourly
Term	≥37	≤ 7 days	15 mg/kg	12 hourly
	≥37	> 7 days	15 mg/kg	8 hourly

Infants and Children [14,16,17]:

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	

There is no evidence to support loading doses of vancomycin in children.

A RCT in children found that it increased the risk of Red Man Syndrome with no significant improvement in target level attainment [10]

3 Dosing and Monitoring in Patients with Renal Impairment

- In patients with impaired renal function, dose according to glomerular filtration rate (GFR) (table below). Advice regarding dosing may be sought from your ward pharmacist, the Senior Pharmacist – Antimicrobial Stewardship (page 6658), or the Medical Microbiologist on-call.
- Therapeutic Drug Monitoring (TDM) 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.

Dose Adjustment for renal impairment in infants and children [11]:

- The following dose adjustments have been recommended based on the patients GFR.
- The following recommendations are based on a usual dose of 60 mg/kg/day rather than 40 mg/kg/day.
- GFR can be estimated by the Schwartz formula:

GFR (mL/min/1.73 m2) = (36.5 × Height in cm) / Creatinine (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)

For dose adjustment in neonates with renal impairment [9, 12, 23]:

- Dose adjustments in neonates are based on **serum creatinine** rather than GFR

Serum Creatinine (micromol/L)		IV Dose	Frequency
≤28 week GA*	>28 weeks GA*		
45 - 62	<62	20 mg/kg/dose	24 hourly
63 - 88	63-80	15 mg/kg/dose	24 hourly
89-124	81-106	10 mg/kg/dose	24 hourly
>124	>106	15 mg/kg/dose	48 hourly

**GA=Gestational age*

4 Preparation and administration for intermittent infusion[13]

	Intermittent Infusion	
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	
Dilution	Peripheral line:	Dilute to ≤ 5 mg/mL with either 0.9% sodium chloride or 5% glucose
	Central Line:	May be diluted to 10 mg/mL with either 0.9% sodium chloride or 5% glucose
	<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***	

- Avoid Extravasation
- 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 Pharmacist 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 for any future doses.

5 Therapeutic Drug Monitoring [14-17]

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

**Steady state concentrations are 4-5 times the half-life of vancomycin.*

- 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	
Non-severe infections:	10 to 20 mg/L
Severe infections*: *(e.g. Bacteraemia, endocarditis, osteomyelitis, 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. Meningitis may require **levels up to 25 mg/L to improve penetration into the CSF*

- If levels are therapeutic vancomycin levels should be monitored weekly and ≥ 24 hours after a dose adjustment
- More frequent vancomycin levels will be required if patient has renal impairment OR on other nephrotoxins (e.g. piperacillin-tazobactam, aminoglycosides, NSAIDs or amphotericin B)
- Vancomycin is renally cleared – monitoring of plasma urea and creatinine concentrations is important in the prevention of toxic vancomycin trough levels.

Recommended subsequent dose adjustments for INTERMITTENT infusion target attainment:

Target Trough	Trough Concentration	Dose Adjustment	
10 to 20 mg/L	≤5 mg/L	Multiply next dose by 2	**Maximum dose increase is 2 g/dose. If the calculated dose is greater than 2 g/dose, increase the dosing interval**
	5 – 6 mg/L	Multiply next dose by 1.75	
	6 – 8 mg/L	Multiply next dose by 1.5	
	8 – 10 mg/L	Multiply next dose by 1.25	
	10 – 20 mg/L	No change	
	>20 mg/L	Withhold further doses and obtain another level after ≥6 hours. Recommence when concentration is <20 mg/L at 50% of the previous dose or by increasing the dosing interval.	
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 p4.*

Therapeutic Drug Monitoring service:
Pharmacokinetic AUC modelling can be done in patients that have difficulty in obtaining therapeutic levels.
Please page the AMS pharmacist during working hours #6658

6 Monitoring renal Function

- Urea and creatinine should be measured at commencement then at least twice weekly while on vancomycin.
- These blood tests may be done when vancomycin levels are taken to reduce the number of venepunctures.

7 Adverse Effects

- Anaphylactic reactions including hypotension, palpitations, sub sternal pressure, tachycardia, wheezing, dyspnoea, urticaria, or pruritus. If this occurs the infusion should be ceased immediately. Once the patient is stabilised may start at a lower infusion rate for subsequent doses. Follow usual procedure for the management of anaphylaxis reactions.
- 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 (associated with persistently elevated trough levels, concurrent nephrotoxins and piperacillin-tazobactam use)
- Reversible haematological abnormalities (neutropenia, eosinophilia, thrombocytopenia)
- Systemic hypersensitivity reactions including nephritis, rash, hepatitis etc.

8 Vancomycin continuous IV infusion[18-22]

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

- Vancomycin exhibits some 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

9 Dosing guideline for continuous IV infusion

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

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

10 Preparation and Administration for Continuous Infusion

	Continuous Infusion
Preparation	Reconstitute vials as for intermittent infusion
Dilution	Dilute to ≤5 mg/mL with either 0.9% sodium chloride and 5% glucose (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

Indication	**Target concentration**
Severe MRSA infections	17 – 25 mg/L*

*This target range is consistent with an AUC of 400-600 mg.h/L based on pharmacokinetic modelling [24]

- Random levels can be taken for therapeutic drug monitoring of continuous infusions
- Levels can be taken 24 hours after starting the continuous infusion
- Vancomycin displays linear pharmacokinetics. Dose adjustments are proportional to the levels measure (see table below)
- If vancomycin level is high, monitor creatinine level if one has not been ordered within the last 24 hours

Vancomycin level must be obtained peripherally

(NOT FROM THE SAME LINE AS THE INFUSION)

Recommended subsequent dose adjustments for CONTINUOUS infusion target attainment:

Target level	**Drug Concentration**	**Dose Adjustment**
17 to 25 mg/L	≤10 mg/L	Multiply dose by 2
	11 – 14 mg/L	Multiply dose by 1.5
	14 – 17 mg/L	Multiply dose by 1.25
	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 50% of the previous dose
After dose adjustment, repeat levels after ≥ 24 hours		

For further information

- Please contact the Antimicrobial Stewardship Pharmacist on pager 6658 or the Infectious Diseases Fellow on pager 6675. The Afterhour's pharmacist may also assist.

Therapeutic Drug Monitoring service:
Pharmacokinetic AUC modelling can be done in patients that have difficulty in obtaining therapeutic levels.
Please page the AMS pharmacist during working hours #6658

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