Vancomycin – intermittent regimen 2020

Newborn use only

Alert	S4 - High risk medicine Antimicrobial Stewardship Team recommends this drug is listed as: Restricted. Continuous infusion regimen optimises achievement of steady state target concentration with fewer dose adjustments and a lower total daily dose in comparison to intermittent regimen.
Indication	Infections due to susceptible strains of Staphylococci (including MRSA), Streptococci, Enterococci, Diptheroids, Listeria monocytogenes, Actinomyces, Bacillus sp
Action	Bactericidal agent which interferes with cell wall synthesis, inhibits RNA synthesis and alters plasma membrane function.
Drug type	Glycopeptide antibiotic.
Trade name	DBL Vancomycin Hydrochloride, Vancocin CP, Vancomycin Alphapharm, Vancomycin AN powder for infusion. Vancomycin Sandoz Vycin
Presentation	Vancomycin hydrochloride 500 mg vial Vancomycin hydrochloride 1000 mg vial
Dose	**Standard dose: 15 mg/kg/dose. Dosing interval as per table below**[24] **Severe sepsis:** Consider giving a loading dose of 20 mg/kg/dose in suspected severe sepsis including MRSA, bone infection, meningitis, endocarditis. However, data in neonates are limited.
Dose adjustment	**Renal Impairment:** • For infants with renal impairment, consider using an antibiotic without nephrotoxicity in consultation with an infectious diseases specialist. • If vancomycin is used, perform a trough level before the 2nd dose. • Adjust the dosage interval[5, 21] to achieve a trough level 10–20 mg/L (higher trough level 15–20 mg/L in severe sepsis). Repeat trough level before the next dose after each dosage adjustment or before every 3rd dose for infants within the target range. **Hepatic impairment:** Not applicable. **Therapeutic hypothermia:** Measure trough concentration prior to 2nd dose.[27] **ECMO:** Current evidence is insufficient to recommend a specific dose adjustment.
Maximum dose	Not applicable
Total cumulative dose	Not applicable
Route	IV
Preparation	**<u>500mg VIAL</u>** Add 10 mL of water for injection to the 500 mg vial to make a 50 mg/mL solution **FURTHER DILUTE** Draw up 2 mL (100 mg of vancomycin) of the above solution and add 18 mL glucose 5% or sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 5 mg/mL. **<u>1g VIAL</u>** Add 20 mL of water for injection to the 1g vial to make a 50 mg/mL solution **FURTHER DILUTE** Draw up 2 mL (100 mg of vancomycin) of the above solution and add 18 mL glucose 5% or sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 5 mg/mL. **<u>Fluid restriction</u>** ***To prepare 10 mg/mL concentration***

Method		Interval
Corrected Gestational Age/Postmenstrual Age	**Postnatal Age**	
< 30^{+0} weeks	0–2 days	18 hourly
< 30^{+0} weeks	3+ days	12 hourly
30^{+0}–36^{+6} weeks	0–14 days	12 hourly
30^{+0}–36^{+6} weeks	15+ days	8 hourly
37^{+0}–44^{+6} weeks	0–7 days	12 hourly
37^{+0}–44^{+6} weeks	8+ days	8 hourly
≥ 45^{+0} weeks	0+ days	6 hourly

	Vancomycin can be diluted to 10 mg/mL solution, however this dilution increases the risk of infusion-related events (see adverse reactions). ***500mg VIAL*** *Add 10 mL of water for injection to the 500 mg vial to make a 50 mg/mL solution* ***Further Dilute*** *Draw up 4 mL (200 mg of vancomycin) of the above solution and add 16 mL glucose 5% or sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 10 mg/mL.* *To prepare 10 mg/mL concentration* ***1g VIAL*** *Add 20 mL of water for injection to the 1g vial to make a 50 mg/mL solution* ***Further Dilute*** *Draw up 4 mL (200 mg of vancomycin) of the above solution and add 16 mL glucose 5% or sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 10 mg/mL.*
Administration	IV infusion over ONE hour. Adequately flush the intravenous lines before and after administration of vancomycin.
Monitoring	Renal function, full blood count, hearing function and serum vancomycin concentrations. Target **trough concentration** 10–20 mg/L Aim for higher trough level of 15–20 mg/L in suspected severe sepsis e.g., MRSA, bone infection, meningitis, endocarditis. **Measure trough vancomycin concentration immediately prior to 3rd dose with the exception of:** 1**.** <29^{+0} CGA weeks – before 2nd dose, 2. therapeutic hypothermia – before 2nd dose and 3. renal impairment – before 2nd dose, but refer to renal impairment section below. **Check concentration prior to the 4th dose after any change in dose or frequency.** Once target trough levels are reached, measure trough levels every 3 days prior to consecutive doses. More frequent monitoring may be required in renal impairment, infants receiving other nephrotoxic drugs or suspected severe sepsis. If a **peak concentration** is required to guide dosing, perform this 1 hour after completion of infusion, and target a peak concentration 20-40 mg/L. [22] **Recommended adjustment based on trough concentration:**

Trough concentration	Daily dose	Frequency Preferred	Example
<5 mg/L	**Increase by 50-75%**	**Increase**	**Current daily dose X 1.5-1.75 = NEW DAILY DOSE**
5-9.9 mg/L	**Increase by 25-50%**	**Increase**	**Current daily dose X 1.25-1.5 = NEW DAILY DOSE**
10-20 mg/L	**No Change**	**-**	**-**
20.1-30 mg/L	**Decrease by 10-30%**	**Decrease**	**Current daily dose X 0.9-0.7 = NEW DAILY DOSE**
>30 mg/L	**WITHOLD DOSE**		
	Repeat trough level 24 hourly until concentration 10-20mg/L	**Decrease**	**Current daily dose X 0.5 = NEW DAILY DOSE**

Changing frequency of administration is preferred against changing dose.
< 5 mg/L − increase total daily dose by 50–75% (i.e. 1.5-1.75 times)) by either increasing frequency (preferred) or increasing each dose.
5–9.9 mg/L − increase total daily dose by 25–50% (i.e. 1.25-1.5 times) by either increasing frequency (preferred) or increasing each dose.
10–20 mg/L − no change in dose required.
20.1–30 mg/L − decrease total daily dose by 10–30% (i.e. 0.9-0.7 times) by decreasing frequency (preferred) or decreasing each dose.
> 30 mg/L − withhold dose. Repeat trough concentration 24 hourly until plasma concentration is 10–20 mg/L, then restart at a dose decreased by 50% (i.e. 0.5 times) by decreasing frequency (preferred) or decreasing each dose.

Example for adjusting dose by increasing / decreasing frequency:
Calculate current total daily dose (e.g. 15 mg 8 hourly = 45 mg/day).
If trough <5 mg/L – Increase total daily dose by 1.5 times (i.e. 45 x 1.5 = 67.5 mg/day) and decide on achieving this total daily dose by either increasing the frequency or increasing the dose. :

	If trough 20.1–30 mg/L - Decrease total daily dose to 0.7 times (i.e. 45 x 0.7 = 31.5 mg/day) and decide on achieving this total daily dose by either decreasing the frequency or decreasing the dose. **Renal impairment** For infants with renal impairment, consider using antibiotic without nephrotoxicity in consultation with an infectious diseases specialist. If vancomycin is used, perform a trough concentration before the 2nd dose, irrespective of corrected gestational age.
Contraindications	Known hypersensitivity to vancomycin.
Precautions	Use with caution in patients with renal impairment or those receiving other nephrotoxic, neurotoxic or ototoxic drugs.
Drug interactions	Neurotoxic and nephrotoxic drugs – concurrent use of these agents may contribute to the additive neurotoxic and nephrotoxic effects. Diuretics – potent diuretics (e.g., furosemide) may add to the ototoxic effect. Neuromuscular blocking agents (e.g. pancuronium, suxamethonium, vecuronium) – vancomycin may enhance neuromuscular blockade. Vancomycin may be combined with an aminoglycoside, cephalosporin or rifampicin for synergistic activity.
Adverse reactions	Infusion-related events: Rapid infusion may cause red man syndrome – a predominately histamine-mediated reaction with pruritus, tachycardia, hypotension and rash. It appears rapidly and usually dissipates in 30–60 minutes, but may persist for several hours. Increasing the infusion time usually eliminates the risk for subsequent doses. Anaphylactic reactions may occur. Severe reactions may require treatment with adrenaline (epinephrine), corticosteroids or oxygen. Phlebitis and tissue irritation and necrosis may occur, especially after extravasation. Intramuscular injection is not recommended. Neurotoxicity, ototoxicity and nephrotoxicity – these are more pronounced with the addition of other medications such as aminoglycosides or furosemide. Neutropenia and thrombocytopenia have been reported in adults. Risk is increased with prolonged therapy >1 week but they appear to be reversible when vancomycin is discontinued.
Compatibility	Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9%. Y site: amino acid solutions and fat emulsions, aciclovir, adrenaline (epinephrine) hydrochloride, amifostine, amiodarone, anidulafungin, atracurium, caspofungin, cisatracurium, dobutamine, dopamine, dexmedetomidine, esmolol, filgrastim, fluconazole, gentamicin, granisetron, hydromorphone, insulin regular, labetalol, linezolid, magnesium sulfate, meropenem, midazolam, milrinone, morphine sulfate, mycophenolate mofetil, noradrenaline (norepinephrine), palonosetron, pancuronium, pethidine, potassium chloride, remifentanil, tigecycline, vecuronium, zidovudine.
Incompatibility	Fluids: No information. Y-site: albumin, aminophylline, azathioprine, beta-lactam antibiotics (eg. penicillins, cephalosporins), bivalirudin, calcium folinate, chloramphenicol, daptomycin, foscarnet, furosemide, ganciclovir, heparin sodium, indometacin, ketorolac, methylprednisolone sodium succinate, moxifloxacin, omeprazole, rocuronium, sodium bicarbonate, sodium valproate, streptokinase, urokinase.
Stability	Administer immediately, discard unused portion of reconstituted solution.
Storage	Store below 25°C. Protect from light.
Excipients	DBL Vancomycin Hydrochloride, Vancocin CP: Disodium acetate.
Special comments	Extravasation may cause tissue necrosis.
Evidence	**Pharmacokinetics/pharmacodynamics:** Vancomycin is water-soluble, has a limited plasma protein binding capacity and is mainly eliminated renally by glomerular filtration, although its elimination is further modulated by renal tubular transport.[1] Vancomycin is active against gram-positive bacteria. *Staphylococcus epidermis*, including methicillin-resistant strains, are inhibited by vancomycin concentrations of 1–4 mg/mL; *Staphylococcus pyogenes*, *Streptococcus pneumoniae*, and *Streptococcus viridans* are susceptible to 2 mg/mL; *Bacillus* spp. are inhibited by 2 mg/mL, and *Clostridium* spp. by 0.39–6 mg/mL.[1]

Pharmacokinetic studies demonstrate variability, which is only in part explained by weight, age, or creatinine level.[1-4] This variability necessitates the use of therapeutic drug monitoring (TDM) of trough concentrations to ensure effectiveness and avoid nephrotoxicity. In contrast, the quantification of peak concentrations may provide no additional monitoring value.[1]
Because vancomycin activity against *S. aureus* is primarily exposure-dependent, the 24-hour area under the concentration-time curve (AUC_{0-24}) divided by the MIC (AUC_{0-24}/MIC) is a better predictor of efficacy. In adults with *S. aureus* MIC values less than 1 mg/ml, trough concentrations >10 mg/ml result in AUC_{0-24}/MIC values >400.[1]
In neonates, an RCT [5] compared intermittent intravenous (IV) dosing using the British Neonatal Formulary (BNF) dosage guideline versus continuous IV [loading dose of 15 mg/kg over 1 hour then continuous infusion:
S creatinine <40 micromol/L & cGA ≥40 = 50 mg/kg/day;
S creatinine <40 micromol/L & cGA <40 = 40 mg/kg/day;
S creatinine 40-60 micromol/L & cGA All = 30 mg/kg/day;
S creatinine >60 micromol/L & cGA All = 20 mg/kg/day.

The target trough level for intermittent IV dosing was 10 to 20 mg/L and steady-state level for continuous IV 15 to 25mg/L. Target concentrations at the first steady-state level was higher for continuous IV compared with intermittent IV (45/53 (85%) vs 21/51 (41%); p <0.001). Fewer dose adjustments were required in the continuous IV. The mean daily dose required to achieve target concentrations was lower with continuous IV (40.6 vs 60.6 mg/kg/day; p=0.01). No nephrotoxicity or red man syndrome occurred in either group. Conclusion: Continuous infusion of vancomycin achieves target concentrations more reliably at a lower total daily dose. [LOE II]
There are few case reports of vancomycin cerebrospinal fluid concentrations with reported CSF penetration rates ranging from 7 to 42%.[1]
For peak-trough dosing of intermittent vancomycin, dosing has typically been designed to achieve a peak concentration 20-40 mg/L and a trough 10-15 or 15-20 mg/L, depending on the severity of the infection and the nature of the pathogen. [22] Peak concentrations >40 mg/L are rarely reported except in infants with impaired renal function. [23] Patients with renal failure and other special subpopulations, such as patients exposed to ECMO or indomethacin, need to be monitored more closely. [23]
Multiple studies of vancomycin use have found that previously recommended dosing regimens often do not achieve designated therapeutic ranges.[24] Overall, population pharmacokinetic models contain sufficient levels of unexplained variability to warrant continued TDM for post hoc dose adjustment to achieve a given pharmacodynamic target concentration.[24] However, an external validation analysis across multiple population pharmacokinetic models found that most models led to 'acceptable' vancomycin concentrations in neonates.[25] The ANMF has adapted the documented regimen of Roberts et al 2014.[24]

Efficacy:
Clinical trials of vancomycin in newborn infants are largely underpowered so the relative efficacy of various antibiotic strategies is unclear. Concerns regarding the potential for antibiotic resistance developing result in recommendations to avoid the use of prophylactic antibiotics and limit the duration of antibiotics where possible.[6, 7]

Treatment of neonatal suspected sepsis: Two RCTs have compared the efficacy of vancomycin to other antibiotics in newborns with suspected sepsis [8, 9] Deville et al 2003 [9] reported 63 neonates randomised 2:1 to linezolid (n = 43) or vancomycin (n = 20) with no significant difference in clinical cure rates (78% vs. 61%; P = 0.196). Cernadas et al 2014 [8] reported 109 newborns randomised to cefazolin (52) or vancomycin (57) with no significant difference in rate of adequate outcome (no clinical signs, negative culture and normal laboratory test: cefazolin 92% versus vancomycin 86%) or mortality (cefazolin 7 (13.5%) versus vancomycin 11 (19.2%); p=0.45).
Gwee et al 2018 [5] compared intermittent intravenous (IV) dosing using the British Neonatal Formulary (BNF) dosage guidance versus continuous IV [loading dose of 15mg/kg over 1 hour then continuous infusion). There was no difference in time to clearance of organism or mortality.

Intraventricular antibiotics for bacterial meningitis in neonates: In a single trial that enrolled infants with gram-negative meningitis and ventriculitis, the use of intraventricular gentamicin in addition to intravenous antibiotics resulted in a three-fold increased RR for mortality compared to standard

	treatment with intravenous antibiotics alone. No trial used intraventricular vancomycin. Based on this result, intraventricular antibiotics as tested in this trial should be avoided.[10] Arnell et al 2007 [11] reported 10 children (0 to 15 years) with intraventricular shunt infections initially treated with IV antibiotics for at least 3 days, but this treatment did not sterilise the CSF. After externalisation of the ventricular catheter, high-dose intraventricular treatment with daily instillations of vancomycin or gentamicin with trough concentrations held at high levels of 7 to 17 mg/L for both antibiotic agents resulted in quick sterilisation of the CSF, a low relapse rate, and survival of all patients. The intraventricular vancomycin dose varied between 1 and 10 mg per day. [LOE IV] **Prevention of infection:** Systematic review of 2 RCTs found prophylactic systemic antibiotics in neonates with a central venous catheter reduces the rate of proven or suspected septicaemia. However, there was no significant difference in mortality, a lack of data on long-term neurodevelopmental outcome and of data pertaining to the potentially significant disadvantages of this approach such as the selection of resistant organisms. The routine use of prophylactic antibiotics in infants with central venous catheters in neonatal units cannot currently be recommended. [12] [LOE I GOR D] Three other RCTs have also reported similar effects of prophylactic vancomycin in infants with or without central lines.[13-15] **Newborn infants with necrotising enterocolitis:** No trial included use of vancomycin.[16] **Prevention of necrotising enterocolitis:** Prophylactic oral vancomycin reduced the incidence of NEC in low birth weight infants. However concerns about adverse outcomes persist, particularly related to the development of resistant bacteria. [17, 18] [LOE II GOR D] **Therapeutic hypothermia (TH):** There are no published data regarding the use of vancomycin during treatment with TH in neonates. A population pharmacokinetic study from children who were being treated with TH post cardiac arrest compared with normothermic controls indicated that in patients with normal renal function vancomycin clearance was reduced by 25%.[27] ANMF group Recommendation: In infants being treated with TH measure a trough concentration immediately prior to the second dose. **Safety:** Risk factors for developing nephrotoxicity are the following: trough concentrations >10 mg/ml, concomitant treatment with aminoglycosides, piperacillin/tazobactam and/or prolonged therapy (>21 days).[1] Other risk factors include high peak concentrations, high total dose, pre-existing renal failure, and concurrent treatment with amphotericin and/or furosemide. However, the role of these factors in the neonatal population is not well-established. Proper vancomycin TDM minimised both glomerular and tubular nephrotoxicity in two studies in children and neonates. In most cases, nephrotoxicity is reversible, even after high doses. In contrast, there is no proven association between TDM and ototoxicity prevention.[1] Gwee et al 2018 [5] compared intermittent intravenous (IV) dosing using the British Neonatal Formulary (BNF) dosage guidance versus continuous IV [loading dose of 15 mg/kg over 1 hour then continuous infusion). No nephrotoxicity or red man syndrome occurred in either group.
Practice points	
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Authors Contribution

Original author/s	David Osborn, Srinivas Bolisetty
Evidence Review	David Osborn
Expert review	Amanda Gwee, Tony Lai, Brendan McMullan, Alison Kesson, Hemalatha Varadhan
Nursing Review	Eszter Jozsa, Kirsty Minter
Pharmacy Review	Jing Xiao, Michelle Jenkins, Cindy Chen
ANMF Group contributors	Nilkant Phad, Himanshu Popat, Angela Williams, Jennifer Martin, John Sinn, Helen Huynh, Wendy Huynh, Bhavesh Mehta, Renae Gengaroli, Carmen Burman, Jessica Mehegan, Thao Tran
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty