Vancomycin – continuous infusion regimen 2020

Newborn Use Only

<table>
<tr><td>Alert</td><td>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.</td></tr>
<tr><td>Indication</td><td>Infections due to susceptible strains of Staphylococci (including MRSA), Streptococci, Enterococci, Diptheroids, Listeria monocytogenes, Actinomyces, Bacillus spp.</td></tr>
<tr><td>Action</td><td>Bactericidal agent which interferes with cell wall synthesis, inhibits RNA synthesis and alters plasma membrane function.</td></tr>
<tr><td>Drug Type</td><td>Glycopeptide antibiotic.</td></tr>
<tr><td>Trade Name</td><td>Vancomycin Sandoz Vycin. DBL Vancomycin Hydrochloride, Vancocin CP, Vancomycin Alphapharm, Vancomycin AN powder for infusion.</td></tr>
<tr><td>Presentation</td><td>Vancomycin hydrochloride 500 mg vial
Vancomycin hydrochloride 1000 mg vial</td></tr>
<tr><td>Dosage / Interval</td><td>Loading dose 15 mg/kg over 1 hour, immediately followed by
Continuous infusion as per the table below:*
<table>
<tr><th>Serum Creatinine (micromol/L)</th><th>Corrected gestational age (CGA)</th><th>Dose</th></tr>
<tr><td><40</td><td>≥40 weeks</td><td>2.1 mg/kg/hour (equivalent to 50 mg/kg/day)</td></tr>
<tr><td><40</td><td><40 weeks</td><td>1.7 mg/kg/hour (equivalent to 40 mg/kg/day)</td></tr>
<tr><td>40–60</td><td>All</td><td>1.25 mg/kg/hour (equivalent to 30 mg/kg/day)</td></tr>
<tr><td>>60</td><td>All</td><td>0.8 mg/kg/hour (equivalent to 20 mg/kg/day)</td></tr>
</table>
Example: 3kg baby at 41 weeks corrected gestational age with serum Cr 37 = 2.1 mg/kg/hour x 3.0 kg = 6.3mg/hour

Measure vancomycin concentration 24 hours (18–30 hours) and 48 hours after the commencement of infusion and then every 3 days.
See dose adjustment in Monitoring section.

Prescription order:
1. loading dose on ONCE ONLY section of the medication chart
2. Infusion dose in mg/kg/hour on fluid chart.</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia - Refer to vancomycin intermittent version.
ECMO- Refer to vancomycin intermittent version.
Renal impairment – Refer to dosing section.
Hepatic impairment – Refer to vancomycin intermittent version.</td></tr>
<tr><td>Route</td><td>IV</td></tr>
<tr><td>Preparation/Dilution</td><td><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 5 mL (250 mg of vancomycin) of the above solution and add 45 mL glucose 5% or sodium chloride 0.9% to make a final volume of 50 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 5 mL (250 mg of vancomycin) of the above solution and add 45 mL glucose 5% or sodium chloride 0.9% to make a final volume of 50 mL with a final concentration of 5 mg/mL.

<u>Special circumstances</u> To prepare 10 mg/mL concentration
For fluid restricted infants, vancomycin can be diluted to 10 mg/mL solution, however this dilution increases the risk of infusion-related events (see adverse reactions).
<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 10 mL (500 mg of vancomycin) of the above solution and add 40 mL glucose 5% or sodium</td></tr>
</table>

<table>
<tr><td></td><td>chloride 0.9% to make a final volume of 50 mL with a final concentration of 10 mg/mL.
To prepare 10 mg/mL concentration
<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 10 mL (500 mg of vancomycin) of the above solution and add 40 mL glucose 5% or sodium chloride 0.9% to make a final volume of 50 mL with a final concentration of 10 mg/mL.</td></tr>
<tr><td>Administration</td><td>Loading dose: IV infusion over ONE hour.
Maintenance infusion: Continuous IV infusion. Change solution every 24 hours.</td></tr>
<tr><td>Monitoring</td><td>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 vancomycin concentration 24 hours (18–30 hours) after commencement of infusion AND 24 hours after each change of infusion rate.
<table>
<tr><th>Level 1
24 hours after commencement</th><th>Dose</th><th>Level 2</th><th>Consecutive levels</th></tr>
<tr><td>15-25mg/mL</td><td>Same</td><td>48 hours
After first level</td><td>Day 6, day 9, day 12, day15
Every 3 days</td></tr>
<tr><td><15mg/mL</td><td>Increase</td><td>24 hours
After dose adjustment</td><td>48 hours if targeted level achieved followed by every 3 days</td></tr>
<tr><td>>25mg/mL</td><td>Decrease</td><td>24 hours
After dose adjustment</td><td>48 hours if targeted level achieved followed by every 3 days</td></tr>
</table>
Repeat steady state level more frequently if
1. 10% change in body weight OR
2. 25% change in serum creatinine OR
3. age-related dose adjustment OR
4. interruption in IV infusion OR
5. infant receives indomethacin.

If vancomycin level <15 or >25 mg/L: Adjust dose using below calculation:
Adjusted dose (mg/kg/hour) = last maintenance dose (mg/kg/hour) x (20mg/mL ÷ last vancomycin concentration)
For example:
1. Last dose was 2.1 mg/kg/hour and the last vancomycin concentration was 12 mg/L: Adjusted dose: 2.1 mg/kg/hour x (20 mg/L ÷ 12 mg/L) = 3.5 mg/kg/hour
2. Last dose was 2.1 mg/kg/hour and the last vancomycin concentration was 28 mg/L: Adjusted dose: 2.1 mg/kg/hour x (20 mg/L ÷ 28 mg/L) = 1.5 mg/kg/hour
Adjustment to > 4.2 mg/kg/hour (100mg/kg/day) should be in consultation with pharmacist and consultant.</td></tr>
<tr><td>Contraindications</td><td>Known hypersensitivity to vancomycin.</td></tr>
<tr><td>Precautions</td><td>Use with caution in patients with renal impairment or those receiving other nephrotoxic, neurotoxic or ototoxic drugs.</td></tr>
<tr><td>Drug Interactions</td><td>Neurotoxic and nephrotoxic drugs – concurrent use of these agents may contribute to the additive neurotoxic and nephrotoxic effects.
Diuretics – potent diuretics (e.g. furosemide [frusemide]) 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</td></tr>
</table>

	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 and oxygen. Phlebitis and tissue irritation with 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 (frusemide). Neutropenia and thrombocytopenia have been reported in adults; risk is increased with prolonged therapy >1 week and 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	Y-site: Albumin, aminophylline, azathioprine, beta-lactam antibiotics (e.g. penicillins, cephalosporins), bivalirudin, calcium folinate, chloramphenicol, daptomycin, foscarnet, furosemide (frusemide), 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. Infusion solution is stable for 24 hours below 25°C.
Storage	Store below 25°C. Protect from light.
Special Comments	If IV infusion is interrupted frequently or for longer periods of time, recommend changing over to intermittent regimen. In severe sepsis, if the IV infusion is interrupted for short duration (e.g. up to 4 hours), consider giving the missed dose over an hour followed by the continuous infusion at the original rate.
Evidence summary	**Pharmacokinetics/pharmacodynamics:** Vancomycin is water-soluble, has limited plasma protein binding 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, is 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, *Corynebacterium* spp. by 0.04–3.1 mg/mL and *Clostridium* spp. by 0.39–6 mg/mL.[1] Pharmacokinetic studies demonstrate variability that is only in part explained by weight, age or creatinine.[1-4] These studies report that current dosage regimens typically achieve therapeutic target ranges for CoNS, MSSA and MRSA with MIC ≤1 microg/mL 50 to 60% of the time.[2] 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 provides no additional monitoring value.[1] Because vancomycin activity is primarily time-dependent, the 24 hour area under the curve ($AUC_{0–24}$) divided by the MIC ($AUC_{0–24}$/MIC) is a better predictor of efficacy. In adults with MIC values less than 1 mg/ml, trough concentrations >10 mg/mL result in AUC_{0-24}/MIC values of >400.[1] The elimination half life of vancomycin has been reported to range from 3.5 to 10 hours, decreasing with increasing gestation and postnatal age, and significantly longer in infants with a

patent ductus arteriosus and with indomethacin treatment. [19]
In neonates, an RCT [5] compared intermittent intravenous (IV) dosing using the British National Formulary (BNF) dosage guidance [15 mg/kg/dose: <29 weeks 24-hourly; 29 to 35 weeks 12-hourly; 36 to 44 weeks 8-hourly; >44 weeks 6-hourly] 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 concentration for intermittent IV dosing was 10 to 20 mg/L and steady state concentration for continuous IV 15 to 25 mg/L. Target concentrations at the first steady state concentration were higher for continuous IV compared with intermittent IV (45/53 (85%) vs 21/51 (41%); p <0.001)). Fewer dose adjustments and a lower total daily dose were required to achieve target concentrations with continuous IV compared to intermittent IV. No nephrotoxicity or red man syndrome occurred in either group. [LOE II]
There are few case reports of vancomycin cerebrospinal fluid concentrations with reported CSF penetration rates ranging from 7 to 42%.[1]

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 reduce the duration of antibiotic therapy where possible.[6, 7]
Treatment of neonatal suspected sepsis: Two RCTs have compared the efficacy of vancomycin with 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). Ceriani 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 15 mg/kg over 1 hour then continuous infusion). There was no difference in time to clearance of organism or mortality although this study was not powered to detect this.

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. There is a lack of data on long-term neurodevelopmental outcome and 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 with 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]

	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 (frusemide). 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	This is the first time the consensus group has introduced a continuous infusion regimen for vancomycin after publication of a RCT comparing continuous and intermittent regimen in newborn infants. [5] A continuous regimen was reported to optimise achievement of steady state target concentrations with fewer dose adjustments and a lower total daily dose compared to an intermittent regimen. However, the participants' mean birth weight (2271 g), gestation at birth (34 weeks) and current weight (2549 g) were relatively higher than populations treated by many perinatal centres. However, there are practical issues in terms of intravenous access for continuous infusion in extremely premature infants. The consensus group considered that whilst continuous infusion has better pharmacokinetic efficacy the group is not able to recommend a preferred regimen. In this revised version, monitoring section has been further improved: Vancomycin level is not a steady state at 24 hours. Half-life varies between 3.5 to 10 hours in newborns and is longer in renal impairment, PDA, indomethacin. Also, a level at 24 hours, then 3 days later as suggested in the previous version may miss some very high steady state levels which could occur after the 50 hour mark. Changes were made in this updated version to address this issue suggesting to measure at 24 hours, then 48 hours and then every 3 days.
References	1. Pacifici GM, Allegaert K. Clinical pharmacokinetics of vancomycin in the neonate: a review. Clinics. 2012;67:831-7. 2. Bhongsatiern J, Stockmann C, Roberts JK, Yu T, Korgenski KE, Spigarelli MG, Desai PB, Sherwin CM. Evaluation of Vancomycin Use in Late-Onset Neonatal Sepsis Using the Area Under the Concentration-Time Curve to the Minimum Inhibitory Concentration >=400 Target. Ther Drug Monit. 2015;37:756-65. 3. Kato H, Hagihara M, Nishiyama N, Koizumi Y, Mikamo H, Matsuura K, Yamagishi Y. Assessment of optimal initial dosing regimen with vancomycin pharmacokinetics model in very low birth weight neonates. J Infect Chemother. 2017;23:154-60. 4. Kim J, Walker SA, Iaboni DC, Walker SE, Elligsen M, Dunn MS, Allen VG, Simor A. Determination of vancomycin pharmacokinetics in neonates to develop practical initial dosing recommendations. Antimicrob Agents Chemother. 2014;58:2830-40. 5. Gwee A, Cranswick N, McMullan B, Perkins E, Bolisetty S, Gardiner K, Daley A, Ward M, Chiletti R, Donath S, Hunt R. Continuous Versus Intermittent Vancomycin Infusions in Infants: A Randomized Controlled Trial. Pediatrics. 2019 Feb 1;143(2):e20182179. 6. Clinical Excellence Commission, 2018, Newborn Antibiotic Guideline for early and late onset sepsis during birth episode of care. Revised June 2018. Sydney: Clinical Excellence Commission. 7. Clinical Excellence Commission, 2018, Paediatric Antibiotic Guidelines for Severe Sepsis & Septic Shock & Unwell Neonates. Revised July 2018. Sydney: Clinical Excellence Commission. 8. Ceriani Cernadas JM, Fernandez Jonusas S, Marquez M, Garsd A, Mariani G. Clinical outcome of neonates with nosocomial suspected sepsis treated with cefazolin or vancomycin: a non-inferiority, randomized, controlled trial. Arch Argent Pediatr. 2014;112:308-14. 9. Deville JG, Adler S, Azimi PH, Jantausch BA, Morfin MR, Beltran S, Edge-Padbury B, Naberhuis-Stehouwer S, Bruss JB. Linezolid versus vancomycin in the treatment of known or suspected resistant gram-positive infections in neonates. Pediatr Infect Dis J. 2003;22:S158-63.

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