

Vancomycin – continuous infusion regimen

Newborn Use Only

2019

Alert	The Antimicrobial Stewardship Team recommends this drug is listed under the following category: 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 the following organisms: Staphylococci (including MRSA), Streptococci, Enterococci, Diptheroids, <i>Listeria monocytogenes</i> , Actinomyces, <i>Bacillus</i> spp.															
Action	Bactericidal agent which interferes with cell wall synthesis, inhibits RNA synthesis and alters plasma membrane function.															
Drug Type	Glycopeptide antibiotic.															
Trade Name	Vancocin CP, Vancomycin Hydrochloride DBL, Vancomycin Alphapharm, Vancomycin Sandoz Vycin.															
Presentation	Vancomycin hydrochloride 500 mg vial Vancomycin hydrochloride 1000 mg vial															
Dosage / Interval	<p>Loading dose 15 mg/kg over 1 hour, immediately followed by Continuous infusion as per the table below:*</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Serum Creatinine (micromol/L)</th> <th style="text-align: center;">Corrected gestational age (CGA)</th> <th style="text-align: center;">Dose</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;"><40</td> <td style="text-align: center;">≥40 weeks</td> <td style="text-align: center;">2.1 mg/kg/hour (equivalent to 50 mg/kg/day)</td> </tr> <tr> <td style="text-align: center;"><40</td> <td style="text-align: center;"><40 weeks</td> <td style="text-align: center;">1.7 mg/kg/hour (equivalent to 40 mg/kg/day)</td> </tr> <tr> <td style="text-align: center;">40–60</td> <td style="text-align: center;">All</td> <td style="text-align: center;">1.25 mg/kg/hour (equivalent to 30 mg/kg/day)</td> </tr> <tr> <td style="text-align: center;">>60</td> <td style="text-align: center;">All</td> <td style="text-align: center;">0.8 mg/kg/hour (equivalent to 20 mg/kg/day)</td> </tr> </tbody> </table> <p style="margin-left: 40px;">E.g. 3 kg baby at 41 weeks corrected gestational age with serum Cr 37 = 2.1 mg/kg/hour x 3.0 kg = 6.3 mg/hour</p> <p>Measure vancomycin concentration 24 hours (18–30 hours) and 48 hours after the start of infusion and then every 3 days. Adjust the dose as per the monitoring section.</p> <p>Doctor’s prescription order: Prescribe (1) loading dose on ONCE ONLY section of the medication chart and (2) infusion dose in mg/kg/hour on fluid chart.</p>	Serum Creatinine (micromol/L)	Corrected gestational age (CGA)	Dose	<40	≥40 weeks	2.1 mg/kg/hour (equivalent to 50 mg/kg/day)	<40	<40 weeks	1.7 mg/kg/hour (equivalent to 40 mg/kg/day)	40–60	All	1.25 mg/kg/hour (equivalent to 30 mg/kg/day)	>60	All	0.8 mg/kg/hour (equivalent to 20 mg/kg/day)
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<40	≥40 weeks	2.1 mg/kg/hour (equivalent to 50 mg/kg/day)														
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>60	All	0.8 mg/kg/hour (equivalent to 20 mg/kg/day)														
Route	IV															
Preparation/Dilution	<p>Add 10 mL of water for injection to the 500 mg vial to make a 50 mg/mL solution. Then:</p> <p>For 5 mg/mL strength (for peripheral lines): Draw up 5 mL of 50 mg/mL solution (250 mg of vancomycin) and add 45 mL of glucose 5% or sodium chloride 0.9% to make a final volume of 50 mL with a final concentration of 5 mg/mL.</p> <p>For 10 mg/mL strength (for central lines and fluid restricted infants): Draw up 10 mL of 50 mg/mL solution (500 mg of vancomycin) and add 40 mL of glucose 5% or sodium chloride 0.9% to make a final volume of 50 mL with a final concentration of 10 mg/mL.</p>															
Administration	<p>For Loading dose: IV infusion over ONE hour.</p> <p>For Maintenance infusion: Continuous IV infusion. Change solution every 24 hours.</p>															
Monitoring	<p>Monitor renal function, full blood count, hearing function and serum vancomycin concentrations.</p> <p>Measure vancomycin concentration 24 hours (18–30 hours) after the start of infusion AND 24 hours after each change of infusion rate.</p> <p>If 24 hour vancomycin concentration is 15–25 mg/L: Repeat steady state level at 48 hours then every 3 days; or earlier if:</p> <ol style="list-style-type: none"> (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. <p>If vancomycin level <15 or >25 mg/L: Adjust dose using below calculation:</p>															

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	<p>Adjusted dose (mg/kg/hour) = last maintenance dose (mg/kg/hour) x (20 ÷ last vancomycin concentration)⁵</p> <p>After dose adjustment, repeat vancomycin concentration after 24 hours until target concentrations are reached.</p> <p>Adjustment to > 4.2 mg/kg/hour (100mg/kg/day) should not be done without discussion with pharmacist and consultant.</p> <p><i>For example, last dose was 2.1 mg/kg/hour and the last vancomycin concentration was 12 mg/L:</i> Adjusted dose = 2.1 mg/kg/hour x (20 mg/L ÷ 12 mg/L) = 3.5 mg/kg/hour</p> <p><i>For example, last dose was 2.1 mg/kg/hour and the last vancomycin concentration was 28 mg/L:</i> Adjusted dose = 2.1 mg/kg/hour x (20 mg/L ÷ 28 mg/L) = 1.5 mg/kg/hour</p>
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	<p>Neurotoxic and nephrotoxic drugs – concurrent use of these agents may contribute to the additive neurotoxic and nephrotoxic effects.</p> <p>Diuretics – potent diuretics (e.g. furosemide [frusemide]) may add to the ototoxic effect.</p> <p>Neuromuscular blocking agents (e.g. pancuronium, suxamethonium, vecuronium) – vancomycin may enhance neuromuscular blockade.</p> <p>Vancomycin may be combined with an aminoglycoside, cephalosporin or rifampicin for synergistic activity.</p>
Adverse Reactions	<p>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.</p> <p>Anaphylactic reactions may occur. Severe reactions may require treatment with adrenaline (epinephrine), corticosteroids and oxygen.</p> <p>Phlebitis and tissue irritation with necrosis may occur, especially after extravasation. Intramuscular injection is not recommended.</p> <p>Neurotoxicity, ototoxicity and nephrotoxicity – these are more pronounced with the addition of other medications such as aminoglycosides or furosemide (frusemide).</p> <p>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.</p>
Compatibility	<p>Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9%.</p> <p>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, remifentanyl, tigecycline, vecuronium, zidovudine.</p>
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	<p>Administer immediately, discard unused portion of reconstituted solution.</p> <p>Infusion solution is stable for 24 hours below 25°C.</p>
Storage	Store below 25°C. Protect from light.
Special Comments	<p>If IV infusion is interrupted frequently or for longer periods of time, recommend changing over to intermittent regimen.</p> <p>In severe sepsis, if the IV infusion is interrupted for short duration (e.g. up to 4 hours), consider</p>

	giving the missed dose over an hour followed by the continuous infusion at the original rate.
Evidence summary	<p>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. <i>Staphylococcus epidermis</i>, including methicillin-resistant strains, is inhibited by vancomycin concentrations of 1–4 mg/mL; <i>Staphylococcus pyogenes</i>, <i>Streptococcus pneumoniae</i>, and <i>Streptococcus viridans</i> are susceptible to 2 mg/mL; <i>Bacillus</i> spp. are inhibited by 2 mg/mL, <i>Corynebacterium</i> spp. by 0.04–3.1 mg/mL and <i>Clostridium</i> 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 \leq1 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 (AUC₀₋₂₄) divided by the MIC (AUC₀₋₂₄/MIC) is a better predictor of efficacy. In adults with MIC values less than 1 mg/ml, trough concentrations >10 mg/mL result in AUC₀₋₂₄/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 \geq40 = 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]</p> <p>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]</p> <p>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.</p> <p>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</p>

	<p>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]</p> <p>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]</p> <p>Newborn infants with necrotising enterocolitis: No trial included use of vancomycin.[16]</p> <p>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]</p> <p>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]</p> <p>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]</p> <p>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.</p>
<p>References</p>	<ol style="list-style-type: none"> 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, Chiletto 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.

	<p>9. Deville JG, Adler S, Azimi PH, Jantusch 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. <i>Pediatr Infect Dis J.</i> 2003;22:S158-63.</p> <p>10. Shah SS, Ohlsson A, Shah VS. Intraventricular antibiotics for bacterial meningitis in neonates. <i>Cochrane Database Syst Rev.</i> 2012.</p> <p>11. Arnell K, Enblad P, Wester T, Sjolin J. Treatment of cerebrospinal fluid shunt infections in children using systemic and intraventricular antibiotic therapy in combination with externalization of the ventricular catheter: efficacy in 34 consecutively treated infections. <i>J Neurosurg.</i> 2007;107:213-9.</p> <p>12. Jardine LA, Inglis GDT, Davies MW. Prophylactic systemic antibiotics to reduce morbidity and mortality in neonates with central venous catheters. <i>Cochrane Database Syst Rev.</i> 2008.</p> <p>13. Baier RJ, Bocchini JA, Jr., Brown EG. Selective use of vancomycin to prevent coagulase-negative staphylococcal nosocomial bacteremia in high risk very low birth weight infants. <i>Pediatr Infect Dis J.</i> 1998;17:179-83.</p> <p>14. Kacica MA, Horgan MJ, Ochoa L, Sandler R, Lepow ML, Venezia RA. Prevention of gram-positive sepsis in neonates weighing less than 1500 grams. <i>J Pediatr.</i> 1994;125:253-8.</p> <p>15. Moller JC, Nelskamp I, Jensen R, Reiss I, Kohl M, Gattermann S, Iven H, Gortner L. Comparison of vancomycin and teicoplanin for prophylaxis of sepsis with coagulase negative staphylococci (CONS) in very low birth weight (VLBW) infants. <i>J Perinat Med.</i> 1997;25:361-7.</p> <p>16. Shah D, Sinn JKH. Antibiotic regimens for the empirical treatment of newborn infants with necrotising enterocolitis. <i>Cochrane Database Syst Rev.</i> 2012.</p> <p>17. Bury RG, Tudehope D. Enteral antibiotics for preventing necrotizing enterocolitis in low birthweight or preterm infants. <i>Cochrane Database Syst Rev.</i> 2001.</p> <p>18. Siu YK, Ng PC, Fung SC, Lee CH, Wong MY, Fok TF, So KW, Cheung KL, Wong W, Cheng AF. Double blind, randomised, placebo controlled study of oral vancomycin in prevention of necrotising enterocolitis in preterm, very low birthweight infants. <i>Arch Dis Child Fetal Neonatal Ed.</i> 1998;79:F105-9.</p> <p>19. de Hoog M, Mouton JW, van den Anker JN. Vancomycin: pharmacokinetics and administration regimens in neonates. <i>Clinical Pharmacokinetics.</i> 2004;43:417-40.</p> <p>20. Australian Injectable Drugs Handbook 7th Edition - AIDH (Australian I.V. Medicines) Accessed 06/12/2018.</p> <p>21. Micromedex online. Accessed 06/12/2018.</p>
Commentary	<p>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 (<i>Pediatrics.</i> 2019 Feb 1;143(2):e20182179).</p> <p>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.</p> <p>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.</p>

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