Vancomycin – intermittent regimen 2024

Newborn use only

Alert	New South Wales Antimicrobial Stewardship category: Restricted after 72 hours. 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	Treatment of potentially life-threatening infections (untreatable with less toxic antimicrobials) including methicillin resistant staphylococcus aureus (MRSA), coagulase negative staphylococcal epidermidis (CONS), Strep. viridans, Strep. bovis, enterococci.
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 powder for infusion, Vancocin CP powder for infusion, Vancomycin Alphapharm powder for infusion, vancomycin Juno powder for infusion, vancomycin viatris powder for infusion. Vancomycin (10mg/mL) 100mg in 10mL sodium chloride 0.9% Baxter syringe.
Presentation	Vancomycin hydrochloride 500 mg vial Vancomycin hydrochloride 1000 mg vial Vancomycin (10mg/mL) 100mg in 10mL sodium chloride 0.9% Baxter syringe.
Dose	**ANMF consensus: Dosing schedule as per table below**[1] **Monitor drug concentrations as per monitoring section.** **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	**Therapeutic hypothermia:** Measure trough concentration prior to 2nd dose[2] and wait for the result before administering the dose. **Renal Impairment:** • For infants with renal impairment, consider using an antibiotic without nephrotoxicity. • If vancomycin is used, measure trough concentration before 2nd dose and wait for the result before administering the dose. • Adjust the dosage interval[5, 21] to achieve a trough concentration 10–20 mg/L. 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. **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%, glucose 10%, 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.

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

	FURTHER DILUTE Draw up 2 mL (100 mg of vancomycin) of the above solution and add 18 mL glucose 5%, glucose 10%, or sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 5 mg/mL. ***<u>Vancomycin 100mg/10mL (10mg/mL) Baxter prefilled syringe</u>*** ***<u>Preparing 5mg/mL concentration</u>*** Draw up 10mL (100mg) of Vancomycin from the 10mg/mL Baxter prefilled syringe and add 10mL of sodium chloride 0.9% to make a final volume of 20mL with a final concentration of 5mg/ml. **<u>Special circumstances (Vancomycin 10 mg/mL concentration- can only be given via central line)</u>** For fluid restricted infants, vancomycin can be diluted to 10 mg/mL concentration. ***<u>Preparing 10 mg/mL concentration using 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 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* ***<u>Preparing 10 mg/mL concentration using 1000mg VIAL</u>*** *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.* ***<u>Vancomycin Baxter prefilled syringe is available as 10mg/mL concentration (100mg/10mL)</u>***
Administration	IV infusion over ONE hour. Adequately flush the intravenous lines before and after administration of vancomycin.
Monitoring	Monitor renal function, full blood count, hearing function and serum vancomycin concentrations. **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. Refer to renal impairment section below. **Target trough concentration** 10–20 mg/L. **After any change in dose or frequency - Check trough concentration prior to 4th dose, except 3 conditions listed above where trough concentrations are required prior to 2nd dose.** 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.[3,4,5] (1, 2) **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**	**-**	**-**

	20.1-25 mg/L	**Decrease by 25-50% and do trough levels prior to next dose.**	**Decrease**	**Current daily dose X 0.5-0.75 = NEW DAILY DOSE**
	>25 mg/L	**WITHOLD DOSE. Repeat trough levels 12 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.
20.1-25 mg/L – decrease total daily dose by 25-50% by decreasing the frequency (preferred) or decreasing each dose.
>25 mg/L – withhold dose. Repeat trough concentration 12 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 26 mg/L - withhold next dose, repeat trough level 12 hourly, once repeat concentration is <20mg/L, decrease total daily dose to 0.5 times (i.e. 45 x 0.5 = 22.5 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. 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 renal impairment or those receiving other nephrotoxic, neurotoxic, or ototoxic drugs.
Drug interactions	Potential ototoxic or nephrotoxic drugs – e.g. amphotericin B, aminoglycosides, piperacillin-tazobactam, concurrent use requires careful monitoring. 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. There have been reports that the frequency of infusion-related events (including hypotension, flushing, erythema, urticaria, and pruritus) increases with the concomitant administration of anaesthetic agents. Infusion-related events may be minimised by the administration of Vancomycin as a 60-minute infusion prior to anaesthetic induction.
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. Reversible neutropenia - usually starting one week or more after onset of therapy with vancomycin. Thrombocytopenia. Pancytopenia – rare. 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. 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.
Overdose	Supportive care. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).
Compatibility	Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9%, glucose 5% in sodium chloride 0.9% Y site: amino acid solutions and fat emulsions, acetaminophen, acetylcysteine, aciclovir, adrenaline (epinephrine) hydrochloride, alfentanil HCL, alprostadil, alteplase, amikacin sulfate, amiodarone, amoxicillin sodium/clavulanate potassium, ampicillin, anidulafungin, atenolol, atracurium, atropine sulfate, azithromycin, buprenorphine, calcium chloride, calcium gluconate, caspofungin, chlorpromazine, cefpirome sulfate, ciprofloxacin, cisatracurium, clarithromycin, clindamycin, codeine phosphate, colistimethate Sodium, cyanocobalamin, cycloPHOSphamide , cyclosporine, dexamethasone sodium phosphate, dexmedetomidine HCL, digoxin, diltiazem HCL, dobutamine HCL, dopamine HCL, doxycycline hyclate, enalaprilat, epinephrine HCL, ertapenem Sodium, erythromycin lactobionate, esmolol, famotidine, fentanyl, filgrastim, fluconazole, fosfomycin, fosphenytoin, gentamicin sulfate, glycopyrrolate, hydromorphone, insulin regular, isoproterenol HCL, ketamine HCL, labetalol, levetiracetam, lidocaine HCL, linezolid, lorazepam, magnesium sulfate, meropenem/veborbactam, metoprolol, metronidazole, midazolam, milrinone, morphine HCL and sulfate, naloxone, nicardipine, noradrenaline (norepinephrine), octreotide, ondansetron, pamidronate disodium, pancuronium bromide, papaverine, pentobarbital sodium, pentoxifylline, phenobarbital sodium, phentolamine mesylate, phenylephrine HCL, Plasma-Lyte, posaconazole, potassium acetate, potassium chloride, procainamide, propranolol HCL, protamine, pyridoxine, ranitidine HCl, remifentanil, sodium acetate, sodium bicarbonate, sodium nitroprusside, succinylcholine, tacrolimus, thiamine, thiotepa, tigecycline, tobramycin, tolazoline, vasopressin, vecuronium, verapamil, voriconazole, zidovudine, zoledronic acid.
Incompatibility	Fluids: No information. Y-site: Albumin, aminophylline, amphotericin B, amphotericin B cholesteryl sulfate complex, amphotericin B lipid complex, amphotericin B liposome, ampicillin sodium/sulbactam sodium, azathioprine, cloxacillin sodium, dantrolene, daptomycin diazepam, diazoxide, epoeitin alfa, fluorouracil, foscarnet, furosemide, ganciclovir, ibuprofen lysine, indometacin, ketorolac, lacosamide, lansoprazole, leucovorin calcium, methylprednisolone sodium succinate, moxifloxacin, omeprazole, oxacillin, phenytoin sodium, sulfamethoxazole/trimethoprim, theophylline urokinase, valproate, warfarin. Caution/variable: Aztreonam, ampicillin sodium, cefamandole, cefazolin, cefepime, cefoperazone, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, heparin sodium, hydralazine, hydrocortisone sodium succinate, imipenem/cilastain, meropenem, pantoprazole, piperacillin sodium, piperacillin sodium/tazobactam sodium, propofol, rocuronium, ticarcillin disodium, ticarcillin/clavulanate,
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

Background

Vancomycin is a water-soluble glycopeptide, 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.[3] 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.[3]

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 (AUC0-24) divided by the MIC (AUC0-24/MIC) is a better predictor of efficacy. Vancomycin, a glycopeptide, is administered to treat (suspected) serious gram-positive infections caused by Staphylococci, including methicillin-resistant Staphylococcus aureus (MRSA) and coagulase-negative Staphylococci (CoNS).[4,5] It is almost exclusively eliminated unchanged by glomerular filtration and to some extent by tubular secretion. The 2020 recommendation by The Infectious Diseases Society of America (IDSA), Paediatric Infectious Diseases Society, and the society of Infectious Diseases Pharmacists recommend a target AUC/MIC of 400-600 in adult population with serious MRSA infections. In their previous 2011 guideline, they recommended higher trough concentration of 15-20 mg/L, but it was associated with nephrotoxicity and 2020 guidelines do not recommend higher trough concentrations of 15-20 mg/L anymore.[1,2] There are limited clinical outcomes data to support any AUC targets for neonatal population. Pharmacokinetics and pharmacodynamics of vancomycin is different in neonates. It is unbound fraction of vancomycin that is pharmacologically active, which could be higher in neonates due to lower amount of serum albumin.[5] Vancomycin disposition in neonates also depends on weight, age, and renal function.[4,5]

Efficacy

Clinical trials of vancomycin in newborn infants are largely underpowered so the relative efficacy of various antibiotic strategies is unclear.

Treatment of neonatal sepsis: Two RCTs have compared the efficacy of vancomycin to other antibiotics (linezolid or cefazolin). There was no significant difference in clinical cure rates in either of these trials.[9,10] Gwee et al 2018 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.[11] For further details, please refer to vancomycin continuous infusion formulary.

NeoVanc consortium is a multicentre European group studying the optimal dosing for vancomycin in neonates. This consortium includes many NICUs from European countries. The standard dosing regimen practised by NeoVanc consortium is in the table below.[12,13]

Corrected Gestational Age/Postmenstrual Age	Interval
$<29^{+0}$ weeks	24 hourly
29^{+0}-35^{+6} weeks	12 hourly
$\geq 36^{+0}$ weeks	8 hourly

NeoVanc group conducted an open-label, multicentre, Phase IIb, randomised, parallel group, non-inferiority trial recruiting participants across 22 NICUs in 5 European countries.[12,13] Infants were randomised in a 1:1 allocation ratio for each regimen. Standard group received 10±2 day course of vancomycin using the dosing regimen given in the table above. Intervention group received a 5±1 day course of loading dose of 25 mg/kg followed 8-12 hours later by a maintenance dose of 15 mg/kg 12 hourly (PMA≤35 weeks) or 8 hourly (PMA>35 weeks). There was no clear benefit with shorter course with loading regimen over the standard regimen. There was also a concern that hearing in the loading dose with shorter duration group had 30% abnormal hearing screening, compared to15% in standard regimen (adjusted risk ratio 1.72; 95% CI 1.0-2.9). Long term follow-up, secondary PK and microbiological outcomes are not yet

available from this study. The findings of this trial do not justify shorter and higher dose regimen in neonates.
ANMF group is reviewing the Neovanc consortium recommendations and awaiting Neovanc group's feedback on target trough concentrations and dose adjustments.
Prevention of infection: A systematic review conducted in both full term and preterm infants found 3 small studies (total number=290 neonates).[14] Two of the studies used vancomycin prophylaxis and 1 study used amoxicillin.[15-17] Cooke 1997 RCT included only VLBW infants.[17] The experimental group in this trial used 5 mg/kg twice a day through the duration of parenteral nutrition/central line. Spafford et al 1994 added vancomycin 25 µg/mL to PN solution to all neonates on PN.[15] Harms et al 1995 used IV amoxicillin 100 mg/kg/day 3 times a day in all neonates with central lines.[16] Meta analysis found that prophylactic antibiotics in neonates with central venous lines decreased the rates of proven bacterial sepsis (typical RR 0.38, 95% CI 0.18-0.82). No resistant organisms were identified in any of the studies. However prophylactic antibiotics had no impact on their primary outcome of mortality. The authors of the review concluded that 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.[14] Three other RCTs, not included in the systematic review reported similar effects of prophylactic vancomycin in infants with or without central lines. A prospective, randomized study by Kacia et al, 1994[19] evaluated the effectiveness of a continuous low-dose vancomycin infusion to prevent nosocomial gram-positive bacteraemia initiated within the first 2 weeks of life in neonates weighing <1500 gm. Seventy-one infants received constant infusion of vancomycin (25/~g/ml) mixed with their total parenteral nutrition solution; 70 infants served as control subjects. Administration of vancomycin was begun at a mean age of 5.4 _+ 2.9 days. Infants had mean serum vancomycin concentrations of 2.4 µg/ml, and received vancomycin for a mean of 11± 7 days. No vancomycin-resistant organisms were detected in surveillance cultures during the 2-year study period. Control group had significantly higher gram positive sepsis, compared to vancomycin group (34% vs 1.4%, respectively.[19] Baier et al, 1998, conducted similar RCT in very low birthweight infants using similar vancomycin dose (25 µg/mL) in PN solution.[20] There was a significant reduction in the number of coagulase-negative staphylococcal (CONS) bacteraemia (defined as isolation of the same organism from two positive blood cultures) during PN (5 vs. 0; P= 0.037) as well as the total number of bacteraemia and fungaemia (9 vs. 1; P= 0.036). The total number of hospital days (108±13 vs. 76±6; P= 0.039) were reduced in infants receiving vancomycin. Infants with birth weights of< 1000 g who received corticosteroids for treatment of chronic lung disease benefitted most from treatment. No vancomycin-resistant strains of CONS or enterococci were detected during the study period.
Intraventricular antibiotics for bacterial meningitis or shunt infections 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.[21] Arnell et al 2007 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.[22] 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. ANMF consensus is not to recommend any intraventricular antibiotic until further trials indicate the safety of these antibiotics via this route.
Treatment of necrotising enterocolitis: No trial included use of vancomycin.[23]
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.[24,25] [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%.[2] 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 include high trough concentrations, concomitant treatment with aminoglycosides, piperacillin/tazobactam and/or prolonged therapy (>21 days).[6] 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.[6]
Practice points	
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