Vancomycin – intermittent regime

Newborn Use Only

2019

Alert	The Antimicrobial Stewardship Team recommends this drug is listed under the following category: Restricted. Continuous infusion is the recommended regime.
Indication	Infections due to susceptible strains of the following organisms: Staphylococci (including MRSA), Streptococci, Enterococci, Diptheroids, *Listeria monocytogenes,* Actinomyces, *Bacillus* 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,
Presentation	Vancomycin hydrochloride 500 mg vial Vancomycin hydrochloride 1000 mg vial
Dosage / Interval	**Standard dose: 15 mg/kg/dose. Dosing interval as per table below**

Corrected gestational age/Postmenstrual age	Interval
$<29^{+0}$ weeks Measure trough levels before 2nd dose	24 hourly
29^{+0}–35^{+6} weeks Measure trough levels before 3rd dose	12 hourly
36^{+0}–44^{+6} weeks Measure trough levels before 3rd dose	8 hourly
$\geq 45^{+0}$ weeks Measure trough levels before 3rd dose	6 hourly

Severe sepsis: Consider giving a loading dose of 20 mg/kg/dose in suspected severe sepsis e.g., MRSA, bone infection, meningitis, endocarditis. However, data in neonates are limited.

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 suspected severe sepsis). Repeat the trough level before the next dose after each dosage adjustment or before every 3rd dose for infants within the target range.

Route	IV
Preparation/Dilution	Add 10 mL of water for injection to the 500 mg vial to make a 50 mg/mL solution. Draw up 1 mL (50 mg) of vancomycin and add 9 mL glucose 5% or sodium chloride 0.9% to make a final volume of 10 mL with a final concentration of 5 mg/mL. In special circumstances, e.g. fluid restricted infants, vancomycin can be diluted to 10 mg/mL, however this dilution increases the risk of infusion-related events (see adverse reactions). To prepare 10 mg/mL concentration: Add 10 mL of water for injection to the 500 mg vial to make a 50 mg/mL solution. Draw up 2 mL (100 mg) of vancomycin and add 8 mL glucose 5% or sodium chloride 0.9% to make a final volume of 10 mL with a final concentration of 10 mg/mL.
Administration	IV infusion over ONE hour.

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 weeks – before 2nd dose and (2) renal impairment – see below. Once target trough levels are reached, measure trough levels every 3 days prior to the dose. More frequent monitoring may be required as follows: in renal impairment, those receiving other nephrotoxic drugs or in suspected severe sepsis. Trough concentration: 10–20 mg/L (aim for higher trough level: 15–20 mg/L in suspected severe sepsis e.g., MRSA, bone infection, meningitis, endocarditis). **Recommended adjustment based on trough concentration:** Adjusted dose (mg/dose) = last maintenance dose (mg/dose) × (target trough concentration ÷ last vancomycin concentration).[5] After dose adjustment, repeat trough levels prior to next dose until target trough levels are reached. Once target levels are reached check trough concentrations every 3 days prior to the dose. *For example, last dose was 45 mg/dose 8 hourly and your target vancomycin trough concentration is 10 mg/L but the last vancomycin trough concentration was 5 mg/L:* *Adjusted dose = 45 mg/dose x (10 mg/L ÷ 5 mg/L)* *= 90 mg/dose 8 hourly* **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 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%, amino acid solution, lipid solution. Y site: aciclovir, amifostine, amiodarone, anidulafungin, atracurium, caspofungin, cisatracurium, dexmedetomidine, esmolol, filgrastim, fluconazole, granisetron, hydromorphone, labetalol, linezolid, magnesium sulfate, midazolam, morphine sulfate, mycophenolate mofetil, palonosetron, pancuronium, pethidine, remifentanil, tigecycline, vecuronium, zidovudine.

Incompatibility	Fluids: No information. Y-site: Beta-lactam antibiotics have been shown to be physically incompatible. The likelihood of precipitation increases with higher concentrations of vancomycin. It is recommended to adequately flush the intravenous lines between the administrations of these antibiotics. Adrenaline (epinephrine) hydrochloride, albumin, aminophylline, azathioprine, 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.
Special Comments	Extravasation may cause tissue necrosis.
Evidence summary	**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] **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] **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.
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