Meropenem

Newborn use only

2023

Alert	The Antimicrobial Stewardship Team recommends this drug is listed under the following category: Restricted. Widespread use of carbapenems has been linked with increasing prevalence of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multi-resistant Gram-negative organisms and *Clostridioides difficile*.
Indication	Severe infections due to multi drug resistant Gram negative organisms e.g., sepsis, intra-abdominal infections or meningitis caused by Extended Spectrum Beta Lactamase (ESBL) producing organisms or carbapenem resistant Enterobacterales (CRE). Note: 1. Meropenem is NOT active against many resistant Gram-positive organisms, such as MRSA and most *Staphylococcus epidermidis*. Vancomycin is first-line therapy for these. Meropenem does have activity against penicillin-susceptible Gram-positive organisms and most anaerobic organisms. 2. An infectious disease specialist and microbiologist should be consulted in the treatment of ESBL or CRE.
Action	Meropenem belongs to carbapenem subgroup of beta-lactam antibiotic. It inhibits cell wall synthesis.(1) Meropenem is a time dependent antibiotic, meaning its bacterial killing effectiveness depends on the amount of **Time (T)** the drug concentration stays above the **Minimum Inhibitory Concentration** (MIC) of the bacteria causing the infection (**T>MIC**).(1) Meropenem is a better choice than imipenem for central nervous system infections. Meropenem attains a higher concentration in the cerebrospinal fluid particularly with inflamed meninges and has a lower incidence of seizures than imipenem.
Drug type	Carbapenem antibiotic
Trade name	Multiple brands are available
Presentation	500 mg vial 1000 mg vial
Dose	40 mg/kg/dose 8 hourly
Dose adjustment	Therapeutic hypothermia: No information. ECMO: No information. Renal impairment(2): GFR mL/min/1.73m^2 30-50 - 20-40 mg/kg dose 12 hourly GFR mL/min/1.73m^2 10-29 - 10-20 mg/kg dose 12 hourly GFR mL/min/1.73m^2 <10 - 10-20 mg/kg dose 24 hourly Hepatic impairment: No information.
Maximum dose	
Total cumulative dose	
Route	IV infusion
Preparation	**<u>Infants <1 kg</u>** Add 9.6 mL of water for injection to 500 mg vial to make a 50 mg/mL solution OR Add 19.1 mL of water for injection to 1 g vial to make a 50 mg/mL solution. **FURTHER DILUTE** Draw up 2 mL (100 mg of meropenem) of the above solution and add 8 mL sodium chloride 0.9% to make a final volume of 10 mL with a final concentration of 10 mg/mL. **<u>Infants≥1 kg or fluid restricted</u>** Add 9.6 mL of water for injection to 500 mg vial to make a 50 mg/mL solution OR Add 19.1 mL of water for injection to 1 g vial to make a 50 mg/mL solution. **FURTHER DILUTE** Draw up 4 mL (200 mg of meropenem) of the above solution and add 6 mL sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 20 mg/mL.

	NOTE: ANMF group acknowledges that dilutions and displacement values vary among the brands. However, the dilution/preparation instructions given in this section are applicable to all brands and the dose difference resulting from displacement volumes of various brands has no significant implication in clinical practice.
Administration	IV infusion over 3 hours.[5,6] Meropenem is recommended to be given as 3-hour infusion, aiming to maximise T>MIC. In very low birth weight infants, where there is limited IV access or there are other competing infusions, the infusion time may be reduced to 30 minutes. However, as soon as the clinical circumstance permits, the infusion time should be reverted to a 3-hour infusion.[4]
Monitoring	Renal function Liver function Full blood count
Contraindications	Hypersensitivity to penicillins, cephalosporins and carbapenems.
Precautions	Renal impairment
Drug interactions	Sodium valproate− meropenem may result in clinically significant reduction in concentration of sodium valproate, which can result in a loss of seizure control.
Adverse reactions	Diarrhoea, rash, vomiting, and glossitis. Hematologic abnormalities, such as agranulocytosis, neutropenia, and leukopenia. Elevated creatinine. Elevated direct bilirubin, aspartate transaminase (AST), alanine aminotransferase (ALT).
Compatibility	Fluids: sodium chloride 0.9% (preferred for stability), glucose 5%, glucose 5% in sodium chloride solution.[5-7] Infusion solutions of 1–20 mg/mL in sodium chloride 0.9% is stable up to 8 hours below 25˚C. Infusion solutions of 1–20 mg/mL in glucose 5% or glucose in sodium chloride solution is stable up to 3 hours below 25˚C.[6] Y-site: Amino acid solutions[5], fat emulsion[5], amikacin, atropine, caffeine citrate, calcium chloride, cefotaxime, ceftazidime, dexamethasone sodium, , digoxin, dobutamine,* dopamine, epinephrine (adrenaline) hydrochloride, fentanyl, fluconazole, furosemide, gentamicin, heparin sodium, hydrocortisone, insulin (regular), magnesium sulfate, metronidazole, morphine, naloxone, norepinephrine (noradrenaline) bitartrate, octreotide, phenobarbital (phenobarbitone), piperacillin sodium-tazobactam sodium, potassium acetate, potassium chloride, sodium bicarbonate. Y-site: At 2.5 mg/mL of meropenem: Anidulafungin, caspofungin, linezolid. *In a simulated Y-site environment, meropenem of 50 mg/mL solution and dobutamine of 12.5 mg/mL solution resulted in precipitation after 4 hours.[5] However, final concentrations of meropenem (10-20 mg/mL) and dobutamine (not more than 5 mg/mL) in our NICU formularies are below these concentrations.
Incompatibility	Fluids: Glucose 10%[5] Y-site: Dolasetron, hydralazine, ketamine, midazolam hydrochloride, phenytoin sodium zidovudine.
Stability	Use immediately after preparation. Diluted solutions are potentially unstable, particularly glucose containing solutions and should be discarded if not used immediately.
Storage	Vial: Store at room temperature
Excipients	Sodium carbonate
Special comments	Meropenem 1 g vial contains 3.92 mmol of sodium
Evidence	**Background** Meropenem is a carbapenem. Carbapenems are beta-lactam antibiotics with a broader spectrum of activity compared to most other beta-lactam antibiotics. Meropenem is somewhat less active against Gram-positive bacteria and more active against Gram-negative bacteria, and anaerobes. Like other beta-lactam antibiotics, carbapenems bind to penicillin-binding proteins, disrupt bacterial cell wall, and thereby kill susceptible micro-organisms. The most important indications for meropenem are

complex infections due to either Gram-negative micro-organisms resistant to cephalosporins or multiple organisms.[8] Meropenem's kill effect is time dependent. For time dependent antibiotics, higher drug concentrations do not result in significantly greater bacterial kill, but a slow continuous kill that is almost entirely related to the time free drug concentration remains above the MIC (T>MIC) during the dosing interval. As a minimum standard for carbapenems, the percentage of the dosing interval that free drug concentration remains above the MIC should be maintained at 40%, but in immunocompromised patients, including neonates, higher targets of 61% to 100% have been suggested to achieve greater cure and bacterial eradication.[1, 9]

Efficacy

Dose optimisation of any antibiotic not only depends on its efficacy but also on safety of the drug. Meropenem is generally well tolerated.[3, 10] A 2014 review by Pacifici et. al., included all studies published on neonates but no conclusion could be drawn on dosing in neonates.[11] Since then, a number of prospective studies reported pharmacokinetics of meropenem in neonates.

Dose studies: A 2020 RCT by NeoMero consortium (NeoMero-1 (neonatal LOS) and NeoMero-2 (neonatal meningitis)) was a randomised, open-label, phase III superiority trial conducted in 18 neonatal units in 6 countries.[12] Infants with (post-menstrual age (PMA) of ≤44 weeks or those with PMA >44 weeks were randomised to receive meropenem or one of the two SOC regimens (ampicillin+gentamicin or cefotaxime+gentamicin) for 8–14 days. In this study, meropenem was given via 30-minute IV infusion at a dose of 20 mg/kg q8h with the exception of those with gestational age (GA) < 32 weeks and PNA <2 weeks who received the same dose q12h with the possibility to increase dosing frequency to q8h from a PNA of two weeks. The primary outcome was treatment success (survival, no modification of allocated therapy, resolution/improvement of clinical and laboratory markers, no need of additional antibiotics and presumed/confirmed eradication of pathogens) at test-of-cure visit (TOC). Stool samples were tested at baseline and Day 28 for meropenem-resistant Gram-negative organisms (CRGNO). The primary analysis was performed in all randomised patients and in patients with culture confirmed LOS. A total of 136 patients (instead of planned 275) in each arm were randomised; 140 (52%) were culture positive. Successful outcome was achieved in 32% in the meropenem arm vs. 23% in the SOC arm (p= 0.087). The respective numbers in patients with positive cultures were 27% vs. 13% (p = 0.022). The main reason of failure was modification of allocated therapy. Treatment emergent adverse events occurred in 72% and serious adverse events in 17% of patients, the Day 28 mortality was 6%. Cumulative acquisition of CRGNO by Day 28 occurred in 4% of patients in the meropenem and 12% in the SOC arm (p = 0.052). Overall, study was underpowered to detect the planned effect.[12]

A 2020 case report by Wu et. al., reported a successful treatment of a preterm neonate with CRE due to K pneumoniae with high dose 40 mg/kg meropenem 12 hourly. This high dose achieved 72%fT>MIC.[13]

A 2022 study by Wu et. al., showed that late onset sepsis due to organisms with a minimal inhibitory concentration (MIC) of 8 mg/L, the doses of 30 mg/kg 3 times daily as a 1-h infusion for newborns with GA ≤ 37 weeks and 40 mg/kg TID as a 3-h infusion for those with GA > 37 weeks were optimal, with PTA (probability of target attainment) of 71.71% and 75.08%, respectively.[14]

ANMF consensus: Applicability of NeoMero study and Wu et. al., study is limited in Australian NICU settings. In Australian NICU settings, antibiotic resistance is not as high and meropenem is reserved for seriously ill neonates with suspected or proven Gram-negative LOS/meningitis. In such cases, efficacy of meropenem should be to the maximum effect, which is attainable in nearly all cases with 40 mg/kg/dose 8 hourly irrespective of gestational age at birth and postnatal age. Meropenem is generally well tolerated. However, when high dose is used, consideration is to be given to other commonly associated factors in severe sepsis such as renal impairment that may affect clearance of meropenem.

Duration of infusion studies: Killing effect of meropenem is produced by the length of time it binds to microorganisms (time dependent antibiotic).[15] Shabaan et. al., in their RCT, of 4-hour vs 30-minute infusion in 102 neonates with culture-proven infection found decreased mortality and ventilator support in 4-hour infusion group.[3] Padari et. al., compared short (30-min) or prolonged (4-h) infusion in 19 very-low-birth-weight (gestational age<32 weeks; birth weight<1,200 g) neonates. Short or prolonged infusions of meropenem were given at a dose of 20 mg/kg every 12 h. They found both 30-

	minute and 4-hour infusion resulted in similar pharmacokinetics in both groups. Likewise, in both groups, free serum drug concentration (fT>MIC was above the MIC (2 mg/L) in nearly 100% of the time.[4] They concluded that 30-minute infusion may be optimal in very low birthweight infants. Numbers in this study were small to draw any definitive conclusions. **ANMF consensus:** Meropenem is to be administered as 3-hour IV infusion. In very low birthweight infants, in whom there can be other competing medicines required to be given via same venous access, meropenem can be administered over 30 minutes. Three-hour infusion is chosen to ensure solution diluted with either sodium chloride 0.9% or glucose 5% is stable in room temperature after preparation (Refer to compatibility section). **Pharmacokinetics:** Meropenem is renally excreted. Clearance of meropenem in neonates is low and can be explained by maturation (weight, postmenstrual age) and renal function (creatinine clearance).[11] There is a knowledge gap in pharmacokinetic (PK) studies of neonates with renal impairment.[2,3] Dose adjustment for renal failure may not be appropriate in cases where severe sepsis is probably responsible for acute renal failure (ANMF consensus) . **Safety** Meropenem is generally well tolerated. Clinical adverse events are very rare. Common adverse effects observed in the paediatric population include diarrhoea, rash, nausea, vomiting, and glossitis. Haematologic abnormalities, such as agranulocytosis, neutropenia, and leukopenia have also been associated with meropenem. Other reported laboratory adverse effects include elevated creatinine, direct bilirubin, aspartate transaminase (AST), alanine aminotransferase (ALT).[7, 16-18] Meropenem associated adverse effects mimic sepsis induced events and the estimation of the probability that a drug caused an adverse clinical event is usually based on clinical judgment. Naranjo Probability Scale is a systematic method to establish causality of an adverse event in such cases.[19]
Practice points	
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