cefEPIME

Newborn use only

2020

Alert	The Antimicrobial Stewardship team recommends this drug be listed as restricted. Aminoglycosides may be inactivated by some penicillin and cephalosporin antibiotics. Where feasible, give at separate sites or separate the administration time of the antibiotics. If this is not possible, flush the line well before and after giving each antibiotic.
Indication	Treatment of infections with serious gram-negative organisms including extended spectrum beta-lactamase (ESBL) producing E. coli and Klebsiella species and Enterobacteriaceae, Pseudomonas species, Citrobacter species and Serratia species.
Action	Fourth-generation cephalosporin with broad-spectrum activity against gram-negative and gram-positive bacteria. Also active against methicillin sensitive staphylococcus aureus and streptococcus pneumoniae. Inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins.
Drug type	Cephalosporin antibiotic.
Trade name	Cefepime Alphapharm, Cefepime Kabi, Cefepime-AFT, Omegapharm Cefepime
Presentation	1g and 2g vial powder for injection
Dose	40 mg/kg/dose 8 hourly (1) (refer to practice points section)
Dose adjustment	Therapeutic hypothermia: No specific information. ECMO: Therapeutic drug monitoring may be beneficial. (2) Renal impairment: Consider adjusting the dosage or interval. (3) Hepatic impairment: No information.
Maximum dose	
Total cumulative dose	No information.
Route	IV
Preparation	Add 8.7 mL of sodium chloride 0.9% or glucose 5% **to 1g** vial to make a 100mg/mL solution OR Add 17.4 mL of sodium chloride 0.9% or glucose 5% **to 2g** vial to make a 100mg/mL solution **Further dilute** Draw up 3 mL (300 mg of cefepime) and add 12 mL of sodium chloride 0.9% or glucose 5% to make a final volume of 15 mL with a final concentration of 20 mg/mL. (Note approximate powder displacement volumes 1g = 1.3mL and 2g = 2.6mL)
Administration	Infuse over 30 minutes (4, 5)
Monitoring	Hypersensitivity reactions, renal function.
Contraindications	Hypersensitivity to cephalosporins or components of the formulation. Contraindicated in patients with severe immediate (IgE mediated) or severe delayed (T-cell mediated) hypersensitivity to penicillins. Seek specialist advice for patients with non-severe immediate hypersensitivity to penicillins.
Precautions	Renal impairment: Mainly excreted renally. Clearance is reduced. (6)
Drug interactions	Other nephrotoxic drugs such as aminoglycosides and potent diuretics such as furosemide. Aminoglycosides may be inactivated by some penicillin and cephalosporin antibiotics. Where feasible, give at separate sites or separate the administration time of the antibiotics. If this is not possible, flush the line well before and after giving each antibiotic. In renal impairment separate the administration of the antibiotics for the longest duration that is practical.
Adverse reactions	Hypersensitivity reactions including anaphylaxis, bronchospasm, urticaria (6) Nephrotoxicity Seizures and encephalopathy
Compatibility	Compatible fluids: Glucose 5%, sodium chloride 0.9%, glucose in sodium chloride solutions, glucose 5% in Hartmann's. (7, 8) Y-site: amikacin, amiodarone, amphotericin B lipid complex, ampicillin, azithromycin, calcium gluconate, dexamethasone sodium phosphate, dexmedetomidine hydrochloride, esmolol hydrochloride, fluconazole, furosemide, gentamicin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, insulin, leucovorin, linezolid, methylprednisolone sodium succinate, metoprolol tartrate, metronidazole, pamidronate disodium, pancuronium bromide, piperacillin sodium/tazobactam sodium, potassium acetate, ranitidine, remifentanil, rocuronium

	bromide, sodium bicarbonate, sulfamethoxazole/trimethoprim, tobramycin sulfate, valproate sodium, vasopressin, zidovudine. Variable compatibility (consult product information, local resources or pharmacist) for: dobutamine hydrochloride, morphine sulfate, vancomycin hydrochloride
Incompatibility	Y-site: acetylcysteine, aciclovir, amphotericin B liposome, ciprofloxacin, ganciclovir, labetalol hydrochloride, magnesium sulfate, mannitol, midazolam hydrochloride, pantoprazole sodium, phenytoin sodium, vecuronium.
Stability	Reconstituted solutions should be used immediately. If necessary, reconstituted solutions are stable for 24 hours at 2 to 8 °C. The solution is clear and colourless to pale yellow or amber. May darken when stored but can still be used
Storage	Cefepime vials should be stored in original cartons below 25°C. Protect from light. Reconstituted solutions are stable for 24 hours at 2 to 8 °C. Protect from light.
Excipients	Arginine.
Special comments	
Evidence	**Efficacy** According to EUCAST (European Committee on Antimicrobial Susceptibility Testing), cefepime's Minimum Inhibitory Concentration (MIC) for P. aeruginosa is 8 µg/mL and for Enterobacter species, is 4 µg/mL, respectively. For S. pneumoniae, Haemophilus influenzae and other pathogens, cefepime's MIC is less than 4 mg/mL. (9) In an open label, prospective pharmacokinetic study in preterm and term neonates <2 months of age by Zhao et al. 2020, (1) found that 78% and 66% of preterm and term neonates respectively, had plasma concentrations above the MIC of 4 µg/mL with the dosing 50 mg/kg/dose 12 hourly. For MIC of 8 µg/mL, they found that 40 mg/kg/dose 8 hourly was required for preterm and term neonates with 80% and 70% of patients achieving the target, respectively. This is different to population pharmacokinetic modelling by Capparelli et al. 2005, suggesting a dosing of 30 mg/kg/dose 12 hourly for postnatal age <14 days, irrespective of gestational age. (4) Pharmacokinetic modelling by Lima-Rogel et al. 2008, suggests a cefepime dose of 250 mg/m^2 (equivalent to 23 mg/kg/dose) every 12 hours for bloodstream infections caused by most gram-negative organisms and a dose of 550 mg/m^2 (equivalent to 49 mg/kg/dose) every 12 hours was suggested for the treatment of infections caused by Pseudomonas sp. in infants younger than 2 months of age. (5). Knoderer et al. conducted a retrospective cohort study in neonates with late-onset sepsis. Mean GA was 29.7 ± 5.8 weeks and mean postmenstrual age was 33 ± 6.2 weeks. The mean empiric cefepime dose was 36 ± 12.6 mg/kg per dose every 12 hours, based on serum creatinine and severity of infection. This regimen resulted in an 81% clinical cure rate and a 100% microbiologic cure rate. (10) <u>ANMF consensus recommendation:</u> 40 mg/kg/dose 8 hourly is recommended as cefepime is generally used as a directed therapy for pseudomonas or empiric therapy for other serious infections. (LOEII, GOR B). This dose recommendation is based on Zhao et al. (1) <u>CSF concentrations:</u> The information for cefepime in CSF is limited. The rate of penetration of cefepime in the CSF was variable with CSF-to-serum ratio ranging between 30% and 87% in preterm neonates, and 3.6% and 59% in term neonates. (6) <u>Renal insufficiency:</u> The serum concentration of creatinine was a strong predictor of cefepime clearance (Cl). Cefepime is mainly excreted unchanged in urine. In neonates, the cefepime Cl value was approximately 40% of that of more mature infants, which results in a longer t1/2 and a higher trough concentration. (6) <u>ECMO:</u> Cefepime clearance was reduced in paediatric patients treated with ECMO. The model demonstrated that the age of the ECMO circuit oxygenator is inversely correlated to central volume of distribution (V1). For free cefepime, only 74% demonstrated a fT_MIC of 16 µg/mL, a chosen target for the treatment of pseudomonal infections, for greater than 70% of the dosing interval.

	Pediatric patients on ECMO might benefit from the addition of therapeutic drug monitoring of cefepime to assure appropriate dosing. (2) **Safety** Arnold et al. compared the safety profile of cefepime to ceftazidime in neonates. The most commonly reported adverse effect was seizures occurring at a rate of 4% on cefepime. (11) Knoderer et al. noted hypophosphatemia in 12.2% of neonates, and overall adverse effects attributable to cefepime were reported in 14.9% of neonates. Hypersensitivity reactions are reported with cephalosporins. There are case reports of seizures and encephalopathy in adults. Dose adjustment has been suggested in renal insufficiency in adults. (3) **Pharmacokinetics** Following a single IV dose, total body clearance averaged 3.3 mL/min/kg and average volume of distribution was 0.3 L/kg. The overall mean elimination half-life was 1.7 hours. The urinary recovery of unchanged cefepime was 60.4% of the administered dose, and renal clearance was the primary pathway of elimination, averaging 2.0 mL/min/kg. (12)
Practice points	Cefepime is generally used as directed or empiric therapy for serious infections, such as pseudomonas infections, and the dosing regimen recommended in this formulary is based on pseudomonal infections.
References	1. Zhao Y, Yao B-F, Kou C, Xu H-Y, Tang B-H, Wu Y-E, et al. Developmental population pharmacokinetics and dosing optimization of cefepime in neonates and young infants. Frontiers in pharmacology. 2020;11:14. 2. Zuppa AF, Zane N, Moorthy G, Dalton HJ, Abraham A, Reeder RW, et al. A population pharmacokinetic analysis to study the effect of extracorporeal membrane oxygenation on cefepime disposition in children. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2019;20(1):62. 3. Barbhaiya RH, Knupp CA, Forgue ST, Matzke GR, Guay DR, Pittman KA. Pharmacokinetics of cefepime in subjects with renal insufficiency. Clinical Pharmacology & Therapeutics. 1990;48(3):268-76. 4. Capparelli E, Hochwald C, Rasmussen M, Parham A, Bradley J, Moya F. Population pharmacokinetics of cefepime in the neonate. Antimicrobial agents and chemotherapy. 2005;49(7):2760-6. 5. Lima-Rogel V, Medina-Rojas E, Del Carmen Milán-Segovia R, Noyola D, Nieto-Aguirre K, López-Delarosa A, et al. Population pharmacokinetics of cefepime in neonates with severe nosocomial infections. Journal of clinical pharmacy and therapeutics. 2008;33(3):295-306. 6. Pacifici GM. Pharmacokinetics of cephalosporins in the neonate: a review. Clinics. 2011;66(7):1267-74. 7. Cefepime. Micomedex online. Accessed on 27 August 2020. 8. Cefepime. Australian injectable drugs handbook, 8th edition. Accessed on 27 August 2020. 9. Testing ECoAS. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.1, 2018. 2019. 10. Knoderer CA, Kaylor DM, Toth ME, Malloy KM, Nichols KR. Characterization of the clinical outcomes with cefepime in a neonatal intensive care unit: a retrospective cohort study. The Journal of Pediatric Pharmacology and Therapeutics. 2018;23(3):209-14. 11. Arnold C, Ericson J, Cho N, Tian J, Wilson S, Chu V. Best Pharmaceuticals for Children Act-Pediatric Trials Network Administrative Core Committee. Cefepime and Ceftazidime Safety in Hospitalized Infants. Pediatr Infect Dis J. 2015;34(9). 12. Cefepime Alphapharm. MIMS online. Accessed on 27 August 2020.

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