cefTRIAXONE
Newborn use only

2023

Alert	The Antimicrobial Stewardship Team has listed this drug under the following categories: Restricted after 72 hours (Amber category) Avoid ceftriaxone for at least 24 hours before or after the administration of intravenous calcium solutions (including parenteral nutrition). Avoid ceftriaxone in neonates with moderate to severe hyperbilirubinemia. Cefotaxime is preferred in these scenarios. (ANMF consensus)[1, 2]
Indication	1. Gonococcal infections: a. Prophylaxis in neonates born to mothers with known but UNTREATED N. gonorrhoeae, b. Treatment of Ophthalmia neonatorum, c. Treatment of localised infection of mucosal surfaces (pharynx, vagina, urethra, anus), d. Treatment of infection at site of scalp electrode, and e. Treatment of disseminated infection (arthritis, sepsis, meningitis) 2. Sepsis and meningitis – As an ongoing/community therapy in cefotaxime responsive sepsis and meningitis in neonates at negligible risk of bilirubin encephalopathy upon consultation with paediatric ID specialist/microbiologist. (ANMF consensus)[3, 4]
Action	Third generation cephalosporin. It is β-lactamase-resistant. It kills bacteria by interfering with the synthesis of cell walls.[5]
Drug type	Cephalosporin Antibiotic.
Trade name	Ceftriaxone viatris (Alphapharm), Ceftriaxone AFT
Presentation	1 g and 2 g powdered vial of Ceftriaxone as Ceftriaxone Sodium
Dose	**NOTE:** 1. Lower end of the dose is recommended in preterm or jaundiced infants. 2. Avoid ceftriaxone for at least 24 hours before or after the administration of intravenous calcium solutions (including parenteral nutrition). **Prophylaxis in neonates born to mothers with known UNTREATED N. gonorrhoeae** SINGLE DOSE OF 25-50 mg/kg[3] (maximum 250 mg)[6] IV or IM **Treatment of gonococcal Ophthalmia neonatorum** SINGLE DOSE OF 25-50 mg/kg[3] (maximum 250 mg)[6] IV or IM **Treatment of localised gonococcal infection of mucosal surfaces (pharynx, vagina, urethra, anus)** SINGLE DOSE OF 25-50 mg/kg[3] (maximum 250 mg)[6] IV or IM **Treatment of gonococcal infection at site of scalp electrode** 25-50 mg/kg[3] (max 250 mg)[6] IV or IM DAILY for 7 days **Treatment of gonococcal arthritis or sepsis** 50 mg/kg IV or IM DAILY for 7 days[4-6] **Treatment of gonococcal meningitis** 50 mg/kg IV or IM DAILY for 10-14 days[4-6] **Sepsis and meningitis - As an ongoing therapy** To discuss with Paediatric infectious diseases specialist. Suggested recommended dose: 50-100 mg/kg/day as a DAILY dose[4,19]
Dose adjustment	Therapeutic hypothermia – No information. ECMO – No information. Renal impairment – No dose adjustment is required.* Hepatic impairment – No dose adjustment is required.* *Note: Dose adjustment is not required unless there are both renal and hepatic failures.[5]
Maximum dose	Meningitis - 100 mg/kg/dose DAILY for neonates over 14 days of age.[19]
Total cumulative dose	
Route	IV infusion

	IV bolus (for severe infection) IM
Preparation	**Intravenous** **IV - Alphapharm/Viatris:** 1g vial: Add 9.6mL WFI = 100mg/mL solution 2g vial: Add 9.2mL WFI = 200mg/mL solution **IV - Ceftriaxone AFT brand:** 1g vial: Add 9.4mL WFI = 100mg/mL solution 2 g vial: Add 8.9 mL WFI = 200mg/mL solution **FURTHER DILUTE: -** **Using 100mg/mL** - Draw up 4 mL (400 mg of ceftriaxone) of solution and add 6 mL sodium chloride 0.9% to make a final volume of 10mL with a concentration of 40 mg/mL solution. **OR using 200mg/mL** - Draw up 2 mL (400 mg of ceftriaxone) of solution and add 8 mL sodium chloride 0.9% to make a final volume of 10mL with a concentration of 40 mg/mL solution. **Intramuscular** **IM- Alphapharm/ viatris:** 1g vial: Add 2.5 mL lidocaine (lignocaine) 1% = 350 mg/mL **IM - Ceftriaxone AFT brand:** 1g vial: Add 2.3mL lidocaine (lignocaine) 1% = 350mg/mL 2g vial: Add 4.6mL lidocaine (lignocaine) 1% = 350mg/mL
Administration	IV Infusion: over 30 minutes. IV bolus (for meningitis/severe infection): slow injection over 5 minutes. IM: Inject deep into a large muscle (e.g. thigh muscle). Do NOT inject into or near major nerves and blood vessels as severe neurovascular damage may occur. DO NOT administer lidocaine (lignocaine) solution intravenously. Avoid administration of calcium containing solutions (e.g. Parenteral nutrition) within 48 hours of the last administration of ceftriaxone.[2]
Monitoring	
Contraindications	Known hypersensitivity to beta-lactam antibiotics. Neonates at risk of bilirubin encephalopathy including neonates with moderate to severe hyperbilirubinemia (e.g. Serum bilirubin >200 umol/L or 12 mg/dL).[4] Calcium containing solutions should not be administered within 48 hours of Ceftriaxone in neonates.[2,7]
Precautions	Neonatal jaundice
Drug interactions	Amikacin: May result in additive nephrotoxic risks. Monitor renal function.
Adverse reactions	1. Hyperbilirubinemia – Ceftriaxone displaces bilirubin from albumin binding sites, thereby increasing the amount of free bilirubin in plasma. Ceftriaxone should not be administered to infants with hyperbilirubinemia. 2. Cholelithiasis and biliary sludge 3. Renal precipitates/concretions 4. Severe haemolytic anaemia 5. Colonisation with resistant bacteria with prolonged therapy. 6. Prolonged bleeding time, diarrhea and skin rash – rare. 7. Transient increase in blood urea nitrogen, serum creatinine, aspartate aminotransferase and alanine aminotransferase – rare
Compatibility	**Fluids :** Glucose 5%, glucose 10%, glucose in sodium chloride solution, sodium chloride 0.9%. **Y-site :** Aciclovir, amifostine, anidulafungin, atracurium, aztreonam, bivalirudin, buprenorphine, ciclosporin, cisatracurium, defibrotide, dexamethasone, dexmedetomidine, digoxin, dopamine, ephedrine sulfate, erythromycin, esmolol , fentanyl, foscarnet, furosemide, glyceryl trinitrate, granisetron , heparin sodium , hydrocortisone sodium succinate, insulin (Novorapid) , lidocaine, methylprednisolone sodium

	succinate, metoclopramide , midazolam, morphine sulfate, noradrenaline (norepinephrine), paracetamol, pethidine, potassium chloride, ranitidine, remifentanil , sodium bicarbonate , sodium nitroprusside , suxamethonium, tigecycline , verapamil , zidovudine.
Incompatibility	**Do not mix ceftriaxone with IV solutions that contain Calcium. Deaths have been reported in neonates.** **Fluids:** Solutions that contain calcium e.g. Hartmann's and Ringer's, parenteral nutrition. **Drugs :** Amikacin, aminophylline, azathioprine, azithromycin, calcium chloride, calcium folinate, calcium gluconate, capreomycin, caspofungin, clindamycin, dobutamine, filgrastim, fluconazole, ganciclovir, gentamicin, haloperidol lactate, hydralazine, imipenem-cilastatin, isavuconazole, labetalol, linezolid, magnesium sulfate, mycophenolate mofetil, pentamidine, promethazine, protamine, sodium ascorbate.
Stability	Reconstituted solution is stable for 6 hours at 25℃ or 24 hours at 2-8℃. Infusion solution: stable for 24 hours below 25 °C and 24 hours at 2-8°C. Solution is slightly opalescent and light yellow to amber coloured solution which may darken over time but can still be used.
Storage	Protect from light. Store below 25°C
Excipients	No excipients. Contains 3.6 mmol/g of Sodium.
Special comments	
Evidence	**Background** Ceftriaxone is a third generation cephalosporin. It is active against most neonatal pathogens including Escherichia coli, Klebsiella species, Enterobacter species, Serratia species, Streptococcus agalactiae, Streptococcus pyogenes, Staphylococcus aureus, and Haemophilus influenzae. It has good penetration in the cerebrospinal fluid, even when the meninges are not inflamed. It is now often used as a simpler alternative to cefotaxime in the treatment of meningitis due to organisms other than Listeria monocytogenes and faecal streptococci (enterococci). It is also used to treat Salmonella typhi infection in countries where this organism is becoming resistant to chloramphenicol, and to treat gonorrhea (Neisseria gonorrhea infection).[5] **Efficacy** **<u>Gonococcal infections</u>** Ceftriaxone, given as a single IM dose (125 mg) in 7 neonates with gonococcal ophthalmia neonatorum resulted in clinical improvement with return of negative cultures in all 7 neonates. Ceftriaxone was diluted with 1% lidocaine in a volume of 0.5 mL.[8] Australasian Society of Infectious Diseases (ASID) 2022 guidelines,[3] Centers for Disease Control and Prevention (CDC) treatment guidelines 2021,[6] Canadian guidelines 2015[9] recommend ceftriaxone in the following scenarios with N. gonorrhoeae: 1. Prophylaxis for infants born to mothers with known **untreated** N. gonorrhoeae – 25-50 mg/kg IV or IM single dose. Maximum dose recommended by CDC is 250 mg. Maximum dose recommended by ASID and Canadian guidelines is 125 mg. 2. Treatment of neonates with localised infections for mucosal surfaces (pharynx, vagina, urethra, anus) – ceftriaxone 25-50 mg/kg (max 125 mg) IV or IM as a single dose. 3. Treatment of ophthalmia neonatorum - ceftriaxone 25-50 mg/kg (max 125 mg) IV or IM as a single dose. Azithromycin is used concomitantly in N. gonorrhoeae conjunctivitis to delay cephalosporin resistance and because co-infection with C. trachomatis is possible. Maximum dose recommended by CDC is 250 mg. 4. Treatment of infection at site of scalp electrode (scalp abscess) – ceftriaxone 25-50 mg/kg (max 125 mg) IV or IM daily for 7 days. 5. Treatment of disseminated infections (arthritis, meningitis, sepsis) - ceftriaxone 25-50 mg/kg (max 125 mg) IV or IM daily for 10-14 days. No maximum dose limit was given by CDC. **<u>Cefotaxime responsive meningitis</u>** Australasian Society of Infectious Diseases (ASID) 2022 guidelines suggest that ceftriaxone may be used as a substitute for cefotaxime in neonates with Group B streptococcus meningitis.[3] Martin et al reported pharmacokinetics of ceftriaxone in 7 neonates (9-30 days) and 7 infants (3-9 months) with meningitis. Neonates younger than 14 days of age were given 50 mg/kg/day and the remaining were

given 100 mg/kg/day. Mean ceftriaxone concentrations in CSF were 2.8 mg/L after 24 hours, exceeding by many times the minimum inhibitory concentration of the common meningitis pathogens.[19]. Mulhall et al studied pharmacokinetics of ceftriaxone in 39 neonates with suspected sepsis.[11] Ceftriaxone was given as a once a day IV or IM 50 mg/kg/day. The dosage provided satisfactory plasma concentration throughout the dosage interval without drug accumulation. No CSF concentrations were measured.

Pharmacokinetics

Ceftriaxone is 85–95% protein bound and competes with bilirubin for albumin binding, displacing bilirubin and increasing levels of free bilirubin. Additionally, 40–45% is excreted unmetabolized by the gallbladder into the bile.[10] There is no significant difference in peak concentration of ceftriaxone following intravenous or intramuscular administration.[11] Ceftriaxone is excreted unaltered almost equally in the bile and urine, so treatment does not normally require adjustment unless there are both renal and hepatic failures.[5] The minimum inhibitory concentrations for 90% of organisms (MIC90s) of ceftriaxone for most neonatal microorganisms is extremely low, e.g. Escherichia coli (MIC_{90} = 0.1 µg/ml), Klebsiella species (MIC_{90} = 0.1 µg/ml), Proteus species (MIC_{90} = 0.2 µg/ml), Enterobacter species (MIC_{90} = 0.3 µg/ml), Serratia species (MIC_{90} = 0.4 µg/ml), Streptococcus agalactiae (MIC_{90} = 0.06 µg/ml) and Staphylococcus aureus (β-lactamase producers) (MIC_{90} = 2 µg/ml). Post-natal age was the single most significant factor affecting pharmacokinetics. Elimination half-life and trough serum concentrations decrease and the clearance increases with increasing the post-natal age.[5] Steele et al. studied the pharmacokinetics of ceftriaxone in 5 full-term neonates 8 to 21 days old and 25 infants aged between 6 weeks to 2 years. Results for neonates were not different from those for older infants.[12] Van Reempts et al. studied the safety of ceftriaxone 50 mg/kg daily infused over 2 min in 80 neonates between 26 and 40-weeks' gestation for empiric management of sepsis.[13] Ceftriaxone was combined with ampicillin for early-onset sepsis and vancomycin for late-onset sepsis. Ceftriaxone was well tolerated; two patients developed hyperbilirubinemia but did not require exchange transfusion. Six neonates (7.5%) were observed to have biliary sludge, which resolved spontaneously in 2 weeks irrespective of TPN status.[13]

Intramuscular (IM) ceftriaxone

There is no significant difference in peak concentration of ceftriaxone following intravenous or intramuscular administration.[11]

Safety

Unconjugated hyperbilirubinemia - Ceftriaxone was thought to significantly displace bilirubin from albumin-binding sites and increase the concentration of unbound or free bilirubin. However, evidence of a bilirubin-displacing effect was mainly derived from in vitro studies and/or indirect methods of free bilirubin measurements.[14-18] A more recent prospective study by Amin et al suggested that home therapy with once-daily intramuscular ceftriaxone may be an alternative option for ongoing management of sepsis in asymptomatic infants with a mild unconjugated hyperbilirubinemia born at term. They evaluated the effect of intravenous (IV) ceftriaxone on free bilirubin concentrations in 27 term infants with unconjugated hyperbilirubinemia. Infants were <7 days old and receiving IV antibiotics for >3 days and resolving hyperbilirubinemia with total serum bilirubin levels between 6 and12 mg/dL by day 4 of life. Intravenous ceftriaxone of 50 mg/kg was given over 45 minutes. Ceftriaxone was not associated with a bilirubin-displacing effect in these infants.[4] However, ceftriaxone should not be given to neonates at risk of developing bilirubin encephalopathy.

Ceftriaxone-calcium interaction: In 2007, the United States Food and Drug Administration (FDA) issued an alert that ceftriaxone and calcium-containing products should not be co-administered to any patient receiving either agent within the previous 48 hours in order to prevent possible end-organ damage secondary to ceftriaxone-calcium precipitation. The FDA warnings were provoked by a report of fatal outcomes in neonates, in whose lungs and kidneys, ceftriaxone-calcium precipitates were discovered. However, the majority of these outcomes were due to a Y-site incompatibility between cetriaxone and calcium administered simultaneously through the same intravenous line. In 2009, FDA modified its warning to recommend that ceftriaxone and calcium-containing products may be sequentially administered in patients older than 28 days if the infusion lines are thoroughly flushed between infusions with a compatible fluid. This was following an analysis of two in vitro studies with neonatal and adult plasma found no direct correlation between the potential for a precipitation reaction with various concentrations of ceftriaxone and calcium, An evaluation study that was done subsequently supported the revised FDA recommendations that patients>28 days old may receive ceftriaxone and calcium sequentially.[2,20]

	Bradley et al reviewed the reported cases that led to safety concerns regarding the concurrent administration of intravenous ceftriaxone and calcium in neonates. They assessed 9 reported cases. Eight of them (7 were ≤2 months of age) represented possible or probable adverse drug events. There were 7 deaths. None of the cases were reported from the United States. All infants received IV ceftriaxone, with dosages of 200 mg/kg per day administered to 3 of 6 infants for whom a dosage was reported. Five infants were preterm, with the youngest born at 30 weeks' gestation. At least 3 infants had received multiple doses of ceftriaxone. They drew the conclusion that the concurrent use of intravenous ceftriaxone and calcium-containing solutions in the newborn and young infant may result in a life-threatening adverse drug reaction. Authors hypothesised that contributing factors could be (1) use of ceftriaxone at dosages higher than recommended, (2) intravenous "push" administration, and (3) administration of the total daily dosage as a single infusion.[21] A subsequent systematic review of the literature published by Donnelly et al concluded that concomitant administration of intravenous ceftriaxone and calcium-containing solutions should be avoided in neonates.[22] **ANMF consensus:** There were serious cardiopulmonary adverse events reported in neonates with concurrent administration of IV ceftriaxone and IV calcium, and therefore a gap of at least 24 hours between IV ceftriaxone and IV calcium (either direct IV calcium or calcium containing solution, e.g. parenteral nutrition) is recommended. It is not yet known whether a combination such as intramuscular ceftriaxone and intravenous calcium or intravenous ceftriaxone and oral calcium be acceptable. **Cholelithiasis and biliary sludge** – Ceftriaxone-associated cholelithiasis is a benign and recovering condition and clinical signs are usually absent. Bor et al prospectively evaluated 38 children aged between 1 month and 17 years who received ceftriaxone as a bolus injection. Abnormal gallbladder sonograms were demonstrated in 36.8% of patients on the 10th day of therapy and cholelithiasis was detected in 28.9% of patients and biliary sludge was detected in 7.9%.[23] In a subsequent study, they showed lower incidence of biliary sludge and cholelithiasis (28%) with 30-minute infusion than the previous bolus injection.[24] **Resistant bacteria -** The overutilization of all cephalosporins has resulted in increased rates of enterococcal superinfections because these microorganisms are not eradicated by this entire class of antibiotic.[5] **Other:** Ceftriaxone increases bleeding time, diarrhea and skin rash. Transient increase in blood urea nitrogen, serum creatinine, aspartate aminotransferase and alanine aminotransferase was observed.[5]
Practice points	
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