<table>
<tr><td>Alert</td><td>The Antimicrobial Stewardship Team recommends this drug is listed under the following category: Unrestricted.
Contains 48 mg of sodium per gram of cefazolin sodium.</td></tr>
<tr><td>Indication</td><td>Treatment of infections caused by susceptible organisms:[1-5]
• Gram positive bacteria: Streptococci and Staphylococci including beta-lactamase producing Staphylococci
• Gram negative bacteria: Escherichia coli and some Klebsiella species, provided these are reported susceptible to cefazolin.
Peri-operative prophylaxis (ANMF consensus)[6-8]</td></tr>
<tr><td>Action</td><td>Bactericidal. Inhibits bacterial cell wall synthesis by binding to one or more penicillin binding proteins.</td></tr>
<tr><td>Drug type</td><td>Antibiotic, First generation cephalosporin.</td></tr>
<tr><td>Trade name</td><td>Cefazolin Sandoz, Cefazolin-AFT, Hospira Cefazolin, Kefzol, Cephazolin Alphapharm</td></tr>
<tr><td>Presentation</td><td>Cefazolin sodium 1 g, 500 mg vials</td></tr>
<tr><td>Dose</td><td>Treatment
<table>
<tr><th>Postnatal age</th><th>Current weight (g)</th><th>Dose</th><th>Interval</th></tr>
<tr><td rowspan="2"><8 days of life</td><td><2000</td><td>25 mg/kg/dose</td><td>12 hourly</td></tr>
<tr><td>≥2000</td><td>50 mg/kg/dose</td><td>12 hourly</td></tr>
<tr><td rowspan="2">≥8 days of life</td><td><2000</td><td>25 mg/kg/dose</td><td>8 hourly</td></tr>
<tr><td>≥2000</td><td>50 mg/kg/dose</td><td>8 hourly</td></tr>
</table>
Peri/post-operative prophylaxis
Confirm with surgeon/infectious diseases specialist to ensure cefazolin is the appropriate choice for prophylaxis.
Dose: Same as above.
Duration: Generally, 24-48 hours.</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic cooling: limited data to suggest any changes
ECMO: Additional dose or priming of cardiopulmonary bypass circuit may be required.[9,10]
Renal impairment:[11,12]
GFR 30 to <50mL/min/1.73m^2: 25-50mg/kg/dose 12 hourly
GFR 10-30mL/min/1.73m^2: 25-50mg/kg/dose 24 hourly
GFR ≤ 10mL/minute/1.73m^2: 25-50mg/kg/dose 48 hourly
Hepatic impairment: limited data to suggest any changes.</td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV infusion (preferable); IV bolus; IM</td></tr>
<tr><td>Preparation</td><td><u>IV Infusion</u>
<u>1g Vial</u>
Add 9.5 mL water for injection to the 1 g vial to make 100 mg/mL solution.
FURTHER DILUTE
Draw up 5 mL (500 mg of cefazolin) and add 15 mL of sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 25 mg/mL.
<u>500 mg Vial</u>
Add 4.8 ml water for injection to the 500 mg vial to make 100mg/ml solution.
FURTHER DILUTE
Draw up 5 mL (500 mg of cefazolin) and add 15 mL of sodium chloride 0.9% to make a final volume of 20 mL with a final concentration of 25 mg/mL.
<u>IV bolus</u>
<u>1gm Vial</u>
Add 9.5 mL water for injection to the 1 g vial to make a 100 mg/mL solution.
<u>500 mg Vial</u>
Add 4.8 ml water for injection to the 500 mg vial to make 100mg/ml solution.
<u>IM</u>:
<u>1g Vial</u>
Add 2.5 mL water for injection to the 1 g vial to make a 330 mg/mL solution.</td></tr>
</table>

	500 mg Vial Add 1.3 ml water for injection to the 500mg vial to make a 330 mg/ml solution.
Administration	IV infusion: Infuse over 30 minutes (10-60 minutes). IV bolus: Slow injection over 5 minutes. IM: Inject deep into large muscle mass.
Monitoring	Serum concentrations are not routinely monitored. Perform renal function, electrolytes and FBC during prolonged (> 10 days) therapy.
Contraindications	History of allergy to cephalosporins, anaphylaxis to penicillin or carbapenem.
Precautions	Sodium restriction — each gram of cefazolin contains 48.3 mg (2.1 mmol) sodium. May increase risk of bleeding due to its effect on clotting factors. Impaired renal function: consider reducing dose as seizures may occur with inappropriately high doses.
Drug interactions	Administration with other drugs, particularly aminoglycosides may increase risk of nephrotoxicity.
Adverse reactions	Thrombophlebitis, pruritus, rash, diarrhoea, nausea, oral candidiasis, pseudomembranous colitis, vomiting, Stevens Johnson Syndrome, *Clostridium difficile* colitis, positive coombs test, eosinophilia, leukopenia, neutropenia, thrombocytopenia, thrombocytosis, blood coagulation disorder, raised liver enzymes, candidiasis, raised urea, creatinine and renal failure.
Compatibility	**Fluids:** Glucose 5%, glucose 10%, glucose in sodium chloride solutions, Hartmann's, sodium chloride 0.9%, water for injections. **Y-site:** , aciclovir, adrenaline (epinephrine) hydrochloride, alfentanil, alprostadil, amikacin sulfate, aminophylline, amphotericin B liposomal, amifostine, anidulafungin, atracurium, atropine, azithromycin, aztreonam, bivalirudin, bleomycin, calcium gluconate, cefoxitin, ceftolozane/tazobactam, ceftazidime, ceftriaxone, ciclosporin, dexamethasone, dexmedetomidine, digoxin, , esmolol, fentanyl citrate, filgrastim, fluconazole, folic acid, furosemide, foscarnet, fosphenytoin sodium, gentamicin sulphate, granisetron, heparin sodium, hydrocortisone sodium succinate, indomethacin sodium, insulin, lidocaine hydrochloride, linezolid, lorazepam, mannitol, meropenem, metaraminol bitartrate, methadone hydrochloride, metoprolol, metronidazole, midazolam, milrinone lactate, morphine sulfate, norepinephrine bitartrate, octreotide, ondansetron, palonosetron, pamidronate disodium, paracetamol, pancuronium, penicillin G, pethidine, phenobarbital sodium, piperacillin, potassium acetate, potassium chloride, propofol, propranolol hydrochloride, remifentanil, rituximab, sodium acetate, sodium bicarbonate, sodium nitroprusside, succinyl choline chloride, thiamine, tigecycline, vasopressin, vecuronium, voriconazole, zoledronic acid. **Caution/variable:** Amiodarone, amino acid solutions, amphotericin B, ampicillin, magnesium sulphate, pantoprazole, rocuronium, vancomycin.
Incompatibility	**Fluids:** No information Y-site: Amikacin, ascorbic acid, azathioprine, calcium chloride, caspofungin, cefotaxime, chlorpromazine, diazoxide, dobutamine, dolasetron, dopamine, erythromycin lactobionate, ganciclovir, gentamicin, haloperidol lactate, hydralazine, isavuconazole, mycophenolate mofetil, pentamidine, phenytoin, promethazine, protamine sulfate, pyridoxine, rocuronium, sulfamethoxazole/trimethoprim, tobramycin.
Stability	Stable for 24 hours below 25°C. However, store at 2 to 8°C and use as soon as possible. Crystals may form if the solution is refrigerated. Redissolve by shaking the vial and warming in the hands.
Storage	Store below 25°C. Protect from light.
Excipients	The product contains no excipients or preservatives.
Special comments	Poor penetration into cerebrospinal fluid therefore not suitable for infections of the CNS. Renally excreted as unchanged drug. Not metabolised. Half-life in neonates is 3 to 5 hours. Cefazolin is highly bound to serum albumin −only the unbound cefazolin is pharmacologically active. Water for injection is the preferred diluent. Crystals may form when cefazolin is reconstituted with sodium chloride 0.9% to a concentration of 330 mg/mL. The crystals formed are small and may be overlooked. Redissolve by warming the vial in hands until the solution is clear.
Evidence	**Efficacy** Cefazolin is administered in neonates mainly for prophylaxis (72%) against bacterial infections. To a lesser extent, it is also used to treat bacterial infections empirically (11%) or therapeutically (17%) following a positive culture of a susceptible bacterium.[1-3]

Perioperative prophylaxis against bacterial infection

Evidence to support use of cefazolin in neonates for prevention of surgical site infection in the perioperative period is limited.[6] This practice is largely based on evidence extrapolated from the studies in older age group which showed significant reduction in the risk of surgical site infection when compared to placebo.[7,8,14-18]

Treatment of infections

Coagulase negative staphylococcus sepsis (CONS)

A randomised control trial compared the efficacy of cefazolin with vancomycin along with amikacin for treatment of a presumed or confirmed late onset neonatal sepsis.[2] Fifty-two infants were randomised to cefazolin arm and 57 to vancomycin arm: cultures were positive in 20 and 22 infants in 2 groups respectively. CONS were identified in 72%, while Staph aureus and Gram-negative bacteria were identified in 15% cultures each. Total duration of treatment was 7-10 days based on clinical response and the type of bacteria isolated. In this study, 92% infants in cefazolin group and 86% infants in vancomycin group were successfully treated. Four infants from cefazolin group were switched to vancomycin group for suboptimal clinical response (n=2) and persistent blood culture positivity (n=2) at 72 hours after commencement of treatment. Mortality rate by sepsis was 4% in cefazolin and 9% in vancomycin group (p= 0.44).[2]

Hemels et al retrospectively reported successful use of cefazolin for management of CONS sepsis in 185 infants over a period of seven years.[3] In this study, median gestational age was 29 weeks and median birthweight was 1180 g. The median age of infants at the onset of sepsis was 10 days. Cefazolin was administered at a dose of 100 mg/kg/day empirically and continued for 7 days if the infants showed clinical response and the isolates were susceptible. Gentamicin was also administered concurrently until CONS was confirmed on a culture. On susceptibility testing, CONS isolates in 14% (23/163) infants were resistant to cefazolin. Irrespective of the susceptibility of the CONS isolates, 87% of infants rapidly responded and were successfully treated with cefazolin. Authors hypothesised that the clinical response despite resistance (mec A-positivity) could be due to low virulence of CONS, prevalence of heteroresistance, affinity for cefazolin to penicillin- binding protein 2a and possibly due to concurrent use of gentamicin until the blood culture results were available.[3,4]

Staphylococcus aureus sepsis

Based on low quality evidence gathered from 14 non-randomised studies in adults, a systematic review and meta-analysis suggested cefazolin to be at least as effective as anti-staphylococcal penicillins in the management of staphylococcus aureus bacteremia including infective endocarditis and localised abscesses. Moreover, cefazolin administration seemed to be associated with less nephrotoxicity compared to anti-staphylococcal penicillins.[5,19]

Safety

Adverse drug reactions from cefazolin use are not common. Hypersensitivity reactions such as skin rash, pruritus, drug fever, anaphylaxis and Stevens-Johnson syndrome have been reported in 1-10% patients receiving cefazolin.[20,21] Due to low prevalence of hypersensitivity reactions, cefazolin is considered safe for clinical use even in most patients with penicillin allergy. In a systematic review, cross-hypersensitivity to cefazolin was noted in 0.6% patients with self-reported penicillin allergy and 3% patients with confirmed penicillin allergy.[22] Antibiotic associated pseudomembranous colitis has been reported in up to 14% patients receiving cefazolin. A single single-dose cefazolin can lead to pseudomembranous colitis and diarrhea may not occur in each case.[20] Although very rare, encephalopathy and seizures may develop in patients on cefazolin therapy particularly if higher doses are used in patients with severe renal insufficiency.[20]

Pharmacokinetics

De Cock et al prospectively studied cefazolin plasma concentrations in 36 neonates using 50 mg/kg/dose 8 hourly regimen. The median current weight of the participants was 2755g and the postnatal age was 9 days.[23] Blood samples were collected at fixed timepoints of 0.5, 2, 4 and 8 hours after the first cefazolin dose and subsequently at 8-hour intervals prior to each scheduled dose. 119 total and unbound plasma concentrations were available and one-compartment model was selected for analysis. Cefazolin was considered to be effective if at least for 60% of the dosing interval the unbound cefazolin plasma concentration was > 8 mg/ml using Monte Carlo simulation. In this study the median total and unbound cefazolin plasma concentrations were 101 and 41 mg/L respectively. In the simulations, serum albumin concentration, postnatal age and weight of infants were identified as the most important covariates contributing to variability in the volume of distribution, drug protein binding and clearance.

	Premature infants have a lower clearance (0.03 L/kg/h) and greater volume of distribution (0.39 L/Kg) for cefazolin compared to older children.[24] Cefazolin has a half-life in neonates is 3 to 5 hours in neonates. It is renally excreted unchanged and the plasma half-life can be significantly prolonged in uremic patients.[11,12] As cefazolin plasma concentrations were relatively high in the study, De Cock et al proposed an individualised dosing regimen for neonates based on postnatal age and current weight.[23] The dosing regimen adopted by the consensus group is largely based on neonatal pharmacokinetic model considered in their study taking into account total and unbound cefazolin concentrations with saturable plasma protein binding.[23-25] A prospective validation of this dosing regimen is needed.
Practice points	
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