



RESEARCH ARTICLE

Clinical Pharmacology of Ceftriaxone in Infants and Children

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Abstract

Ceftriaxone is a versatile and useful third-generation β -lactam-resistant cephalosporin. It is given intravenously or intramuscularly once a day. This antibiotic is active against some important gram-positive and most gram-negative bacteria. Ceftriaxone distributes widely in body tissues and in body fluids and penetrates into the cerebrospinal fluid and it is used to treat bacterial meningitis. In 34 infants and children aged 1 month to 19 years with bacterial meningitis, ceftriaxone cured 88% of subjects and the overall clinical response was 96%. Ceftriaxone may be used to treat nasopharyngeal, gonococcal ophthalmia, and epiglottitis. Ceftriaxone is associated with biliary, renal, and haemolytic adverse events in children. Ceftriaxone displays bilirubin from albumin binding sites, thereby increases the amount of unconjugated bilirubin in infants and this drug is not recommended in neonates < 6 weeks old at risk of developing unconjugated hyperbilirubinaemia. Concurrent administration of ceftriaxone and calcium is contraindicated. Ceftriaxone extensively binds to plasma proteins. In neonates, the ceftriaxone concentration slowly decays in plasma, after intravenous administration of 50 mg/kg ceftriaxone, the plasma ceftriaxone concentrations ($\mu\text{g/ml}$) are 155, 147, and 110 at 0.25, 1, and 7 hours, respectively, after administration. The half-life of ceftriaxone is age-dependent and is longer in infants than in children. After intravenous administration, the plasma ceftriaxone concentrations are significantly higher than after intramuscular administration 0.25 and 0.5 hours after administration. Some bacteria may become resistant to ceftriaxone. The aim of this study is to review the published data on effects, pharmacokinetics, and bacterial-resistance of ceftriaxone in infants and children.

Keywords: Ceftriaxone, Effects, Adverse events, Pharmacokinetics, Bacterial-resistance, Infants, Children

Introduction

Ceftriaxone is a versatile and useful “third-generation” cephalosporin that only needs to be given once a day. Ceftriaxone is a β -lactam-resistant cephalosporin first patented in 1979 that is active against some important gram-positive and most gram-negative bacteria. Because of good cerebrospinal fluid penetration, 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 gonorrhoea (*Neisseria gonorrhoea* infection). 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. It has a longer half-life than other cephalosporins; the plasma half-life falls from 15 hours at birth to a value only a little in excess of that found in adult (7 hours) over some 2-4 weeks. Ceftriaxone crosses the placenta and also appears in amniotic fluid. There is no evidence of teratogenicity in animals, but little information regarding its safety during human pregnancy is available. Very little appears in breast milk. It should only be given with great caution to any infants with a high unconjugated bilirubin level. Ceftriaxone can displace bilirubin from its plasma albumin binding sites, thereby increasing the amount of free unconjugated bilirubin. This initially made many clinicians reluctant to recommend its use in neonates < 6 weeks old, and this drug should not

be used in neonates at risk of developing unconjugated hyperbilirubinaemia if a lower than usual threshold is adopted for starting phototherapy. High doses of ceftriaxone often cause a transient precipitate to form in the biliary tract, and small asymptomatic renal stones occasionally form with sustained use. Ceftriaxone has very occasionally caused severe neonatal erythroderma (red neonate syndrome) [1].

Ceftriaxone is active against *Escherichia coli*, *Klebsiella*, *Proteus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Citrobacter*, *Enterobacter*, *Serratia*, *Neisseria gonorrhoea*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Bacteroides* species [2].

Ceftriaxone is used to treat sepsis and disseminated gonococcal infection and meningitis caused by *Escherichia coli*, *Pseudomonas*, *Klebsiella*, *Haemophilus influenzae* and gonococcal infections. For gonococcal infection give 50 mg/kg every 24 hours. For meningitis give 100 mg/kg loading dose, then 80 mg/kg every 24 hours. Ceftriaxone distributes widely (i.e. cerebrospinal fluid, bile, bronchial secretion, lung tissue, ascitic fluid, and middle ear). Monitoring is recommended for blood urea nitrogen, complete blood count, eosinophilia, thrombocytosis, leukopenia, serum electrolytes, creatinine,

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aspartate aminotransferase, alanine aminotransferase, and bilirubin. Concurrent administration of ceftriaxone and calcium-containing solution is contraindicated. Ceftriaxone is incompatible with aminophylline, azithromycin, calcium chloride, calcium gluconate, caspofungin, fluconazole, and vancomycin [3].

Literature search

The literature search was performed electronically using PubMed database as search engine, the cut-off point was March 2019. The following key words: “ceftriaxone infants effects”, “ceftriaxone children effects”, “ceftriaxone infants metabolism”, “ceftriaxone children metabolism”, “ceftriaxone infants pharmacokinetics”, “ceftriaxone children pharmacokinetics”, “ceftriaxone infants resistance”, and “ceftriaxone children resistance” were used. In addition, the books “Neonatal Formulary” [1] and “NEOFAX” by Young and Mangum [3] were consulted. The manuscript was prepared according to the “Instructions for Authors”.

Results

Ceftriaxone diffusion into cerebrospinal fluid of infants and children

Latif and Dajani [4] evaluated the diffusion of ceftriaxone into the cerebrospinal fluid of 27 infants and children with meningitis who were receiving conventional antimicrobial therapy. Ceftriaxone was administered as a single dose of 75 mg/kg and was given early or late or both in the course of the illness. Three hours after a dose, the mean cerebrospinal fluid ceftriaxone concentration was 5.7 µg/ml in patients studied early in the course of meningitis and 2.1 µg/ml in patients studied later in the illness. The diffusion of ceftriaxone did not correlate with the leukocyte count or the protein or glucose content of the cerebrospinal fluid. The present findings indicate that ceftriaxone diffuses sufficiently and consistently into the cerebrospinal fluid to warrant its assessment in the treatment of meningitis.

Efficacy and safety of ceftriaxone in infants and children

Fifty-seven infants and children were treated with once daily ceftriaxone. After an initial loading dose of 100 mg/kg ceftriaxone, the patients received 80 mg/kg as a single daily dose [5]. Etiologic agents included: *Haemophilus influenzae* type b, N = 37 (11 β-lactamase-positive); *Neisseria meningitidis* (N = 11); *Streptococcus pneumoniae* (N = 6); *Streptococcus pyogenes* (N = 1); *Haemophilus influenzae* type f (N = 1); and Group B *Streptococcus* (N = 1). All patients showed clinical improvement and all were bacteriologically cured. Satisfactory cerebrospinal fluid bactericidal activity and drug concentrations were seen 24 hours after a dose in those patients in whom repeated spinal taps were carried following the last dose of therapy. Ceftriaxone, when given in a single daily dose, appears safe and effective in the treatment of bacterial meningitis in neonatal infants and children.

Thirty-four patients aged 1 month to 19 years were treated with ceftriaxone for suspected bacterial meningitis. The overall

bacterial cure was 88%, with an overall clinical response of 96% [6]. No side effects requiring cessation of therapy was observed. Ceftriaxone proved to be safe and effective in the treatment of serious infections in children.

Treatment of bacterial meningitis with ceftriaxone in infants and children

Swann, et al. [7] identified 259 culture-positive isolates from 259 infants aged ≤ 2 months, in whom the most common pathogens were Group B *Streptococcus* (45.0%), *Streptococcus pneumoniae* (21.7%), and nontyphoidal *Salmonella enteric* (11.7%). One hundred and ninety-one isolates were from young infants aged > 7 days and ≤ 2 months. In this group, the most common isolates were *Streptococcus pneumoniae* (41.9%), Group B *Streptococcus* (19.9%), and nontyphoidal *Salmonella enteric* (17.8%). More isolates were more susceptible to ceftriaxone than to the combination of penicillin and gentamicin (99.1% versus 91.8%, Fisher’s exact test P-value = 0.006). In particular, gram-negative isolates were significantly more susceptible to ceftriaxone than gentamicin (97.3% versus 85.1%, Fisher’s exact test P-value = 0.020). Penicillin and gentamicin provided less coverage for gram-negative than gram-positive isolates (86.0% versus 95.1%, X = 6.24, P-value = 0.012). In view of these results, the WHO recommendations for empiric penicillin and gentamicin for suspected neonatal meningitis should be reevaluated.

Craig, et al. [8] studied the efficacy of ceftriaxone in the treatment of childhood bacterial meningitis in a general paediatric unit. Six-two children received 100 mg/kg daily for seven days. Outcome was defined by parameters including mean time to fever defervescence, prolonged fever, days in hospital, seizures, and other acute neurological sequelae, requirement, requirement for ventilation, mortality, and morbidity. Audiology was performed at six weeks and again at three months if abnormal. Neurodevelopment assessment was performed at three months. The mortality rate was 4.8%. Two children had clinically detectable neurological sequelae at three month assessment. The mean duration of stay in hospital was 8.7 nights. Mild self limiting diarrhoea occurred in 19% of children. Ceftriaxone is an effective, safe and well tolerated antimicrobial for the treatment of childhood meningitis. It compares favourably with other equipotent antimicrobials.

Streptococcus pneumoniae is now the predominant pathogen causing meningitis. The resistance of *Streptococcus pneumoniae* to penicillin and third-generation cephalosporins has grown steadily. Waisbourd-Zinman [9] assessed the antibiotic susceptibility of *Streptococcus pneumoniae* isolated from the cerebrospinal fluid of children with meningitis and determined the antibiotic regimen appropriate for suspected bacterial meningitis in Israel. *Streptococcus pneumoniae* isolates from the cerebrospinal spinal fluid were tested for susceptibility to penicillin and ceftriaxone. Of the 35 isolates, 17 (48.6%) showed resistance to penicillin (MIC ≥ 0.12 µg/ml). Only 3 isolates (8.6%) showed intermediate resistance to ceftriaxone (MIC 0.5 µg/ml and < 2 µg/ml), and none showed complete resistance to ceftriaxone (MIC ≥ 2 µg/ml). The rates

of antibiotic resistance were higher in children with antibiotics prior admission (penicillin 88.9% versus 34.6%, P -value = 0.007; ceftriaxone 22.2% versus 3.8%, P -value = 0.015).

In a prospective Swiss multicenter study, 119 children aged three weeks to 15.5 years with acute bacterial meningitis were treated with single daily doses of ceftriaxone (100 mg/kg on days one and two and 60 mg/kg thereafter) [10]. All children were randomly assigned to either short course (4 -7 days), or full courses (8-14 days) therapy depending on whether they had contracted meningococcal, Haemophilus influenzae type b, or pneumococcal meningitis. Bacteriological cure was obtained in 92 (77.3%) children who fully completed the study. Complete clinical recovery was noted in 105 of 119 (88%) children and was as frequent in the short course (91%) as in the full course (89%). All children survived. The present results suggest that short course treatment of acute bacterial meningitis in children with single daily ceftriaxone monotherapy is as efficacious as full course therapy and at least as well tolerated.

Treatment of bacterial meningitis with once daily administration of ceftriaxone in infants and children

A total of 33 children with bacterial meningitis were treated with a single daily dose of 100 mg/kg ceftriaxone for a median duration of 13 days [11]. Pathogens isolated were Haemophilus influenzae type b (N = 15), Neisseria meningitidis (N = 7), Streptococcus pneumoniae (N = 2), group B streptococcus (N = 1), Streptococcus viridians (N = 2), and Staphylococcus epidermidis (N = 6). All cerebrospinal fluid ceftriaxone levels even at the end of the dosing interval were at least 10-fold higher than the MICs of the respective bacterial isolates. Within 12-46 hours after the first dose cultures were sterile in all cases. Side effects encountered were diarrhoea, exanthema, neutropenia, and transient elevation of glutamic oxaloacetic transaminase, but none caused a change of therapy. No child died. Ceftriaxone can be recommended as a safe and effective antibiotic agent for once daily treatment of bacterial meningitis in children.

Fifty-two children were enrolled to evaluate and compare short- versus standard-length ceftriaxone therapy for bacterial meningitis in children [12]. The duration of the short-course regimens were 4-7 days for Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae, respectively. The standard-length regimen was twice as long. Ceftriaxone was given intravenously once daily in a dose of 60 mg/kg after an initial loading dose of 100 mg/kg. Bacteriological and clinical response was comparable. Hearing loss occurred in 3 children in the standard-length group and in no children in the short-course group. Diarrhoea was the only side effect and occurred in 14% of the children. The present results indicate that the short-duration regimen was adequate for the treatment of meningitis caused by the three major meningial pathogens.

Ceftriaxone was given as a single daily intravenous dose of 100 mg/kg on day one, followed by 80 mg/kg daily [13]. A total of 22 children were treated, of whom 14 had

Haemophilus influenzae type b, five children had Streptococcus pneumoniae, and three children had Neisseria meningitidis isolated from their cerebrospinal fluid. The cerebrospinal fluid of all children became sterile within 24-48 hours after ceftriaxone administration. The cerebrospinal fluid ceftriaxone concentrations 24 hours after dosing were 10 to 100-fold higher than the MIC of the pathogenic bacteria early in therapy, and 50-fold higher than the MIC at the end of therapy.

Different dosages of ceftriaxone to treat bacterial meningitis in infants and children

Molyneux, et al. [14] compared the efficacy of 5 and 10 days of parenteral ceftriaxone for the treatment of bacterial meningitis in children. A multicountry, double-blind, placebo-controlled, randomised equivalence study of 5 versus 10 days of treatment with ceftriaxone in children aged 2 months to 12 years with purulent meningitis caused by Streptococcus pneumoniae, Haemophilus influenzae type b, or Neisseria meningitidis. Children (N = 496) received ceftriaxone for 5 days, and 508 children received ceftriaxone for 10 days. In the 5-day group, two children (one infected with HIV) had a relapse; there were no relapses in the 10-day group. A 5 days of ceftriaxone treatment, the antibiotic can be safely discontinued.

Twenty-six children received a single dose of ceftriaxone, 50 mg/kg, for a variety of bacterial infections including abscesses (N = 5), periorbital cellulites (N = 5), bacteraemia without focus (N = 4), osteomyelitis (N = 2), pneumoniae (N = 2), pyelonephritis (N = 2), and otitis media (N = 1) [15]. Organisms isolated from infectious foci were Staphylococcus aureus (N = 9), Streptococcus pneumoniae (N = 6), Streptococcus pyogenes (N = 3), Escherichia coli (N = 2), and Haemophilus influenzae type b, nontypable Haemophilus influenzae, group B streptococcus, Pasteurella multocida, Haemophilus parainfluenzae, and satelliting streptococcus (N = 1 each). Microbiologic cure was achieved in 91% infections, and clinical cure in 96% of children. Seventeen children received ceftriaxone, 75 mg/kg, in two divided doses for a similar variety of infections. Once a day dosing of ceftriaxone in paediatric patients provides greater ease of administration combined with efficacy equal to that achieved with a divided dosage schedule.

Treatment of nasopharyngeal bacteria flora with ceftriaxone in infants

The increasing prevalence of drug-resistance bacteria is attributed to the extensive use of antibiotics which causes selective pressure on the nasopharyngeal flora. Shortened courses of antibiotics have been proposed to decrease the development of resistant strains. Heikkinen, et al. [16] determined the effect of a single dose of 50 mg/kg ceftriaxone on the nasopharyngeal bacteria flora in 167 infants, the median age was 13 months, suffering from acute otitis media. Nasopharyngeal samples for bacterial culture were obtained before and 5 days after treatment with ceftriaxone. Before treatment, Moraxella catarrhalis was isolated in 99 (59%) infants, Streptococcus pneumoniae in 87 (52%) infants, and

Haemophilus influenzae in 53(32%) infants. After treatment, Moraxella catarrhalis was found in 62 (37%) infants, which constitutes a 37% decrease in the colonization rate by this pathogen (P -value < 0.001). Streptococcus pneumoniae was isolated in 50 (30%; 43% decrease) and Haemophilus influenzae in 17 (10%, 68% decrease) infants after treatment (P -value < 0.001 for both). Before treatment, 60% of pneumococcal isolates were sensitive to penicillin, 26% were of intermediate susceptibility, and 14% were penicillin-resistant. Eradication of Streptococcus pneumoniae occurred mainly in infants with penicillin-sensitive isolates. A single dose of ceftriaxone resulted in significant changes in the nasopharyngeal bacteria flora, increasing the relative prevalence of pneumococcal strains with decreased susceptibility to penicillin.

Haiman, et al. [17] compared the effect of one dose and three doses of intramuscular ceftriaxone regimens on the nasopharyngeal carriage of Streptococcus pneumoniae in infants with nonresponsive acute otitis media treated with a 3-day and 1-day regimens of intramuscular ceftriaxone. In a prospective study, 170 infants aged 3 to 36 months with nonresponsive acute otitis media were randomized to receive 1 (N = 83) - or 3 (N = 87)-day intramuscular ceftriaxone regimen (50 mg/kg per day), respectively. On day 1 nasopharyngeal Streptococcus pneumoniae carriage was found in 108 (64%) infants, 54 in each treatment group. Forty-seven of 54 (87%) and 9 of 54 (17%) Streptococcus pneumoniae isolates from the one dose group were nonsusceptible to penicillin and ceftriaxone, respectively; the respective values in the three dose group were 49 of 54 (91%) and 8 of 54 (15%). From 8 to 54 (15%), On days 4 and 5 negative nasopharyngeal cultures were achieved in 43 of 83 (52%) and 70 of 87 (80%) cases from the one dose and three dose group, respectively (P -value < 0.001). Eradication of penicillin-nonsusceptible Streptococcus pneumoniae was achieved on day 4 to 5 in 18 of 49 (37%) and 39 of 49 (80%) organisms isolated from the one dose and three dose groups, respectively (P -value < 0.001). A decrease was observed during the study period in the proportion of highly penicillin-resistant Streptococcus pneumoniae isolated in the three dose group compared with the one dose group (30, 24, 17 and 13% vs. 30, 27, 19 and 26% at days 1, 4 to 5, 11 to 14 and 28 to 30, respectively; P -value = 0.05). The 3-day intramuscular ceftriaxone regimen was significantly superior to the 1-day regimen in the reduction of carriage during the treatment period.

Treatment of gonococcal ophthalmia which ceftriaxone in neonates

Laga, et al. [18] conducted a randomized clinical trial comparing a single intramuscular dose of 125 mg of ceftriaxone with a single intramuscular dose of kanamycin followed by topical gentamicin for seven days, in the treatment of gonococcal ophthalmia in neonates. Of 122 neonates with culture-proved gonococcal ophthalmia, 105 returned for follow-up. Sixty-one infants (54%) received ceftriaxone, 32 infants received kanamycin plus topical gentamicin, and 29 infants received kanamycin plus topical tetracycline. Sixty-six (54%) of the

Neisseria gonorrhoea isolates were penicillinase producing. All 55 newborns that received ceftriaxone and returned were clinically and microbiological cured. These authors conclude that 125 mg of ceftriaxone as a single intramuscular dose is a very effective therapy for gonococcal ophthalmia in neonates, with marked efficacy against extraocular infection and without the need for concomitant topical antimicrobial therapy.

Treatment of Haemophilus influenzae epiglottitis with ceftriaxone in children

Epiglottitis in childhood are caused by Haemophilus influenzae type b. In a prospective, randomized trial, the efficacy of a short course (two days) of ceftriaxone was compared with that of five days of chloramphenicol for the treatment of epiglottitis [19]. The ability of these treatment regimens to eradicate Haemophilus influenzae type b from the throat was also studied. Fifty-five children were enrolled over an 18 month period. Fifty-three (96%) of 55 patients had Haemophilus influenzae type b from at least one site: 44/52 (85%) from blood cultures, 41/47 (87%) from throat swab, and 6/8 (75%) as Haemophilus influenzae type b urinary antigen. Children were randomized to receive either ceftriaxone 100 mg/kg intravenously followed by a single dose of 50 mg/kg 24 hours later (28 patients), or chloramphenicol 40 mg/kg intravenously, then 25 mg/kg eight hourly for five days, intravenously then by mouth (27 patients). A short course of ceftriaxone was successful in treating all patients with no significant side effects and no relapses were observed. A short course of ceftriaxone is a safe, efficacious, and economic alternative to the standard treatment in children with epiglottitis.

Adverse effects of ceftriaxone in infants and children

General considerations: Different types of adverse reactions are reported to be induced by ceftriaxone. All adverse events registered in the Iranian pharmacovigilance database from 1998 through 2009 were screened for ceftriaxone-related adverse events [20]. The extracted data were categorized based on patients' demographics and previous history of allergic to antibiotics. Ceftriaxone was responsible for the highest number of deaths in the Iranian database (49 cases). Of 20,877 reports, 1,205 (5.8%) were related to ceftriaxone. The high number of serious cases makes it necessary to develop preventive measures for reducing those adverse events. These authors recommend an alternative antibiotic, if possibly, in the case of a positive history of allergic reactions to cephalosporins, penicillin and/or other β -lactam antibiotics. Severe and life-threatening adverse reactions induced by ceftriaxone are of great concern.

Ceftriaxone-associated biliary adverse events in children:

A prospective study was conducted in 156 children admitted for the treatment of various infections with different daily ceftriaxone doses (50 mg/kg, 75 mg/kg, and 100 mg/kg). Sonographic examinations of the gallbladder and urinary tract were performed before treatment on the third and seventh day of therapy, and at the first and second month after the

end of treatment [21]. Abnormal gallbladder sonograms were demonstrated in 27 children (17%); 16 of them (10%) had gallbladder lithiasis, 11 (7%) children had gallbladder sludge (N = 4) on the third day, and N = 23 on the seventh day). One child developed urolithiasis (0.6%). Five children (19%) were older and treated with higher drug doses than those with normal sonographic findings (P-value < 0.01 and < 0.05, respectively). Biliary pseudolithiasis (and infrequently nephrolithiasis) usually occurs in children receiving high doses of ceftriaxone.

Ozturk, et al. [22] prospectively evaluated the incidence of biliary sludge and pseudolithiasis in children treated with ceftriaxone. Thirty-three children treated with ceftriaxone for prophylaxis (N = 13) or for an infection (N = 20) were enrolled. The ultrasonographic evaluations were performed before treatment and on the 14th - 5th days and 8th - 10th days of treatment. Nineteen children developed pseudolithiasis and sludge in the gallbladder. It is emphasized that when gallstone and/or sludge are detected in the gallbladder in children by ultrasonographic examination, the administration of ceftriaxone must be sought beyond other causative factors.

Palanduz, et al. [23] used sonography to investigate the incidence and outcome of biliary complications in children receiving ceftriaxone therapy. Ceftriaxone was administered intravenously at a dose of 100 mg/kg per day for 1-3 weeks to 118 children hospitalized for severe infections. Twenty children (17%), all asymptomatic, demonstrated sonographic abnormalities: 8 had gallbladder sludge, without associated acoustic shadowing, and 12 had pseudolithiasis, defined as echogenic material with acoustic shadowing. These abnormalities spontaneously resolved within 2 weeks of stopping the ceftriaxone (mean time to disappearance, 8.2 ± 3.4 days). Ceftriaxone-associated biliary pseudolithiasis is usually asymptomatic and was rapidly reversible after cessation of therapy.

Ceran, et al. [24] prospectively evaluated the incidence and clinical importance of pseudolithiasis in paediatric surgical children receiving ceftriaxone treatment. Fifty children who were given ceftriaxone were evaluated by serial abnormal sonograms. Of these, 13 (26%) developed biliary pathology. After cessation of the treatment, pseudolithiasis resolved spontaneously within a short period.

A total of 151 children who had ceftriaxone therapy for probable or definite bacterial enteritis were prospectively evaluated by serial abdominal ultrasonography [25]. All patients received a dose of ≥ 50 mg/kg per day and for duration of 3 or more days. Five children developed gallbladder precipitates or pseudolithiasis during treatment.

A prospective study was conducted during 1997 in 34 children admitted for the treatment of acute pyelonephritis. Ceftriaxone (intravenous single-dose of 50 mg/kg) was initially used [26]. A first gallbladder sonogram, performed before the first or second injection, was normal in all cases. A second evaluation was performed before the fifth and last injection. On this

second evaluation, the presence of one (N = 3, 8.8%) or two gallstones was recorded in 5 children (15%) on a sonogram made after 3 (N = 4, 11.8%) or 5 (N = 1, 2.9%) injections. Their median age was 7 years. The present findings confirm the possibility of precocious biliary lithiasis under ceftriaxone therapy in childhood and their spontaneous dissolution after discontinuous of ceftriaxone.

Bor, et al. [27] determined the frequency of biliary sludge and cholelithiasis with ceftriaxone therapy. Thirty-eight children aged 1 month to 17 years were evaluated with ultrasonography at the initiation of ceftriaxone therapy and 10th day off therapy, consequently. Abnormal gallbladder sonograms were demonstrated in 36.8% (N = 14) of children at the 10th day of therapy. Cholelithiasis was detected in 28.9% (N = 11) of children and biliary sludge was detected in 7.9% (N = 3) children. Reversible biliary sludge or pseudocholelithiasis due to ceftriaxone treatment is not a rare condition. Therefore it is benign, spontaneously resolved and clinical signs are usually absent.

Ceftriaxone-associated renal adverse events in children:

Li, et al. [28] evaluated the clinical profile, treatment, and outcome of ceftriaxone-associated postrenal acute renal failure in children. The average time of ceftriaxone administration before postrenal acute renal failure was 5.2 days. Ultrasound showed mild hydronephrosis (25/31). Nine children recovered after 1 to 4 days of pharmacotherapy. Twenty-one children were resistant to pharmacotherapy underwent retrograde ureteral catheterization. After catheterization of their ureters, normal urine flow was observed, and symptoms subsided immediately. Ceftriaxone was verified to be the main component of the calculi in 4 children by tandem mass spectrometric analysis. Ceftriaxone therapy in children may cause postrenal acute renal failure.

Shen, et al. [29] evaluated the clinical outcomes in managing acute kidney injury resulting from ceftriaxone-induced urolithiasis with emergency treatment. A series of 15 children aged 4.76 ± 3.74 years were hospitalized. A chief complaint of anuria was present in 12 (80.0%) children for 20 hours to 10 days. All of them were diagnosed post-renal acute kidney injury resulting from ceftriaxone-induced urolithiasis and underwent emergency hospitalization. Double-J stenting with cystoscopy was successfully performed in 9 children (60%), and ureteroscopy was applied in four children (26.7%). One child (6.7%) underwent unilateral double-J inspection combined with contralateral percutaneous nephrostomy, and one (6.7%) child underwent open surgery. All children were followed-up for 11 months-5 years (mean 33.80 ± 22.56 months). No one turned to irreversible renal failure. Ceftriaxone could result in urolithiasis in children, which could also cause acute kidney injury.

Urinary tract calculi have been reported to account for between 1 in 1,000 and 1 in 7,600 hospital admissions in the USA. The annual incidence of urolithiasis in children older than 10 years is 109 per 100,000 of the population in men and 36 per 100,000 of the population in women in Minnesota.

The use of various medications is considered to be one of etiological factors of nephrolithiasis [30]. Ceftriaxone is a widely used and it is generally considered very safe, but complications such as nephrolithiasis have rarely reported in children. Children were treated with 75 mg/kg intravenous ceftriaxone. The first renal ultrasonography was performed on the first or second day of admission and was repeated on the last day of treatment. Stone-forming children underwent metabolic kidney stone risk factor evaluation. They evaluated 284 children with pyelonephritis. The first ultrasonography was normal in all children. On the second ultrasonography metabolic risk factors could not be identified in stone-forming children. The present findings suggest that ceftriaxone-treated children may be at an increased risk of kidney stone formation. Stones passed spontaneously in all affected children so the use of ceftriaxone can be safely continued.

Ceftriaxone may bind with calcium ions and form insoluble precipitate leading to biliary pseudolithiasis. Avci, et al. [31] assessed whether ceftriaxone associated nephrolithiasis develops by the same mechanism, and whether this condition is dose-related. The study involved 51 children with various infections and received 100 mg/kg per day ceftriaxone divided into two equal intravenous doses. The other 27 children received a single daily intramuscular injection of 50 mg/kg. Post-treatment ultrasound identified nephrolithiasis in 4 children (7.8%). The stones were all of small size (2 mm). The renal stones disappeared spontaneously in three of four cases, but were still present in 1 child 7 months after treatment. The present findings show that taking a 7 day course of normal or high dose of ceftriaxone may develop small sized asymptomatic renal stones.

Ceftriaxone-associated haemolysis in children: Over the last decade, second and third generation cephalosporins have been the most common drugs causing haemolytic anaemia. Of these cases, 20% have been attributed to ceftriaxone [32]. The clinical presentation of ceftriaxone-induced haemolytic anaemia is usually abrupt with sudden onset of pallor, tachypnea, cardio-respiratory arrest, and shock. Acute renal failure has been reported in 41% of such cases with a high fatality rate. Boggs, et al. [33] reported the case of a young girl treated with intravenous ceftriaxone who subsequently developed ceftriaxone-induced autoimmune haemolytic anaemia and renal failure. Vehapoglu, et al. [34] reported a case of life-threatening ceftriaxone-induced haemolytic anaemia in a previously healthy 3-year-old girl. Her haemoglobin dropped from 10.2 to 2.2 g/dl over 4 hours, indicating that this girl had life-threatening haemolysis after an intravascular dose of ceftriaxone who had previously been treated with ceftriaxone in intramuscular form for six days.

Schuettpelez, et al. [35] reported the case of one-year-old female with sickle cell disease who survived a brisk and profound haemolytic reaction, resulting in haemoglobin of 0.4 g/dl, after ceftriaxone infusion. Ongoing haemolysis was abrogated with aggressive supportive care, but the girl suffered extensive neurologic sequelae as a result of the event. Serologic testing confirmed the presence of ceftriaxone antibodies.

Kakaiya, et al. [36] described a patient with severe haemolysis that subsided once ceftriaxone was discontinued. Serologic techniques demonstrated immune complex-mediated ceftriaxone-dependent red cell antibodies. These findings were further supported by the results of flow cytometry, in which a change in basal red cell autofluorescence was seen in the presence of the antibody and the drug.

A 5-year-old girl, with no underlying immune deficiency or hematologic disease, was treated with ceftriaxone for a urinary tract infection [37]. After receiving ceftriaxone intramuscularly, massive haemolytic anaemia developed. Laboratory studies showed the presence of an antibody against ceftriaxone, and the findings reflected immune complex type haemolysis.

Ceftriaxone displays bilirubin from albumin binding sites:

Determination of free bilirubin, erythrocyte-bound bilirubin and unconjugated bilirubin was used to test the effects of ceftriaxone on the binding of bilirubin to albumin [38]. This study, performed on blood samples from icteric neonates, showed that the addition of ceftriaxone produced an increase of free bilirubin and erythrocyte-bound bilirubin and a decrease of unconjugated bilirubin. Ceftriaxone displays a significant displacing effect at concentrations obtained during therapeutic use and should be used with caution in high-risk jaundiced infants.

The in-vivo bilirubin-albumin binding interaction of ceftriaxone was investigated 14 non-jaundiced newborns, aged 33-42 weeks of gestation, during the first few days of life [39]. Ceftriaxone (50 mg/kg) was infused intravenously over 30 min. The competitive binding effect of ceftriaxone on the bilirubin-albumin complex was estimated by determining the reserve of albumin concentration at baseline, at the end of ceftriaxone infusion, and at 15 and 60 min thereafter. Immediately after the end of ceftriaxone administration, the reserve albumin concentration decreased from 91.9 ± 25.1 mmol/l to 38.6 ± 10.1 mmol/l (P -value = 0.0001). At the same time the plasma bilirubin toxicity index increased from 0.64 ± 0.40 before ceftriaxone infusion to 0.96 ± 0.44 thereafter (P -value = 0.0001). The highest displacement factor was calculated to be 2.8 ± 0.6 at the end of infusion. Average total serum bilirubin concentrations decreased from a baseline value of 59.6 ± 27.0 mmol/l to 55.2 ± 27.1 mmol/l (P -value = 0.026). Sixty min after the end of ceftriaxone infusion, the reserve albumin was 58.3 ± 21.7 mmol/l, the plasma bilirubin toxicity index regained baseline, but displacement factor was still 1.9 ± 0.2 . The present results demonstrate a significant competitive interaction of ceftriaxone with albumin in-vivo. Thus, ceftriaxone should not be given to neonates at risk of developing bilirubin encephalopathy.

Concurrent administration of ceftriaxone and calcium-containing solutions or products in neonates is contraindicated: In September 2007, the FDA issued an alert recommending that ceftriaxone and calcium-containing solutions should not be administered to any patient within 48 hours of each other. Ninety-four surveys representing

94 hospital systems were included in the analysis [40]. Approximately half (N = 49, 52%) of respondent institutions enacted at least one drug-use policy change based on the warning. Institutions' final interpretations of the warning differed slightly from initial understanding of the warning, and there was an overall minor decrease in the perceived use of ceftriaxone. The majority of those surveyed (N = 70, 74%) estimated that their respective institutions devoted between 1 and 49 employee hours to address the warning.

In April 2009, the FDA retracted a warning asserting that ceftriaxone and intravenous calcium products should not be co-administered to any patients to prevent precipitation events leading to end-organ damage [41]. A search of the FDA Adverse Event Reporting System was conducted to identify any ceftriaxone-calcium interactions that resulted in serious adverse events with ceftriaxone-calcium and 99 events with ceftriaxone-calcium were defined. For ceftriaxone-calcium related adverse events, 7.7% and 20.2% of events were classified as probable and possible for embolism, respectively.

Eight of the reported cases (7 were aged ≤ 2 months) of concomitant administration of ceftriaxone and calcium represented possible or probable adverse drug events [42]. There were 7 deaths. The dosage of ceftriaxone that was administered to 4 of 6 infants, for whom this information was available, was between 150 and 200 mg/kg per day. The concurred use of ceftriaxone and calcium-containing solutions in newborns and young infants may result in life-threatening adverse events.

Appropriate volumes of 2% (W/V) calcium chloride solution were added to 0.4-2 mg/ml ceftriaxone isotonic sodium chloride solution, to make solutions with a final calcium ion concentration of 1.25 mmol/l [43]. A white precipitate could be observed visually when the ceftriaxone concentration of the sample solution was 7 mg/ml.

Ceftriaxone is not metabolized and it is eliminated unchanged by both biliary (40%) and renal mechanisms [1-3]. In literature, there is no data on the metabolism of ceftriaxone in infants and children.

Pharmacokinetics of ceftriaxone in infants and children:

The unbound percentage of ceftriaxone in plasma was measured in 5 infants 7 to 15 months old and in 5 young

children 24 to 70 months old. The unbound percentage of ceftriaxone was 15.7 ± 3.1 in infants and 16.4 ± 13.2 in young children [44]. The pharmacokinetics of ceftriaxone were examined in 39 neonates who required antibiotics for clinically suspected sepsis [45]. The mean neonate gestational age and birth weight were 31.7 ± 4.0 weeks and 1.88 ± 0.86 kg, respectively. Ceftriaxone was administered as a once daily dose of 50 mg/kg by the intravenous or intramuscular route. Ceftriaxone was assayed in 49 series of blood samples, 3 samples of cerebrospinal fluid and 15 samples of urine by a microbiological technique. Blood specimens were collected before and 0.25, 0.5, 1, 3, 7, 12, and 24 hours after ceftriaxone administration. The plasma was isolated from blood and used to assess the ceftriaxone pharmacokinetics. Table 1 shows the plasma ceftriaxone concentrations after the first injection and after multiple intravenous and intramuscular injections of ceftriaxone, and table 2 summarizes the ceftriaxone pharmacokinetic parameters. After single and multiple ceftriaxone administrations, the plasma ceftriaxone concentrations were higher after intravenous than intramuscular administration at 0.25 and 0.5 hours after ceftriaxone dosing. The ceftriaxone pharmacokinetic parameters were not different after intravenously and intramuscularly administrations. The ceftriaxone clearance increased with increasing postnatal age and body temperature (P -value < 0.0002) and decreasing plasma creatinine concentration (P -value < 0.005). Increasing plasma protein concentration was associated with a decrease in distribution volume (P -value < 0.001). A once daily administration of 50 mg/kg ceftriaxone by the intravenous or intramuscular routes provides satisfactory plasma concentrations throughout the dosage interval. Hayton and Stoeckel [46] studied the age-associated changes in ceftriaxone pharmacokinetics and the resulted are reported in Table 3.

Del Rio, et al. [47] reported the susceptibility to ceftriaxone of 4 bacteria recovered from the cerebrospinal fluid cultures of 32 children and the results are summarized in Table 4. These authors measured the ceftriaxone concentrations in the cerebrospinal fluid of children after a ceftriaxone single dose of 50 mg/kg and after multiple doses (Table 5). Multiple doses of ceftriaxone were administered to 12 infants and children with meningitis. In all patients, the initial 75 mg/kg dose of ceftriaxone was followed by 50 mg/kg dose given intravenously every 8 or 12 hours. Peak plasma ceftriaxone

Table 1: Plasma ceftriaxone concentrations ($\mu\text{g/ml}$) following intravenous and intramuscular administration to 49 neonates. The figures are the mean \pm SD, by Mulhall, et al. [45].

			Time after administration (hours)						
	Route	Number of neonates	0.25	0.5	1	3	7	12	24
First dose	IM	6	67 \pm 16	110 \pm 47	120 \pm 32	143 \pm 19	128 \pm 28	89 \pm 21	54 \pm 19
	IV	12	155 \pm 41	150 \pm 40	147 \pm 47	138 \pm 32	110 \pm 34	87 \pm 37	55 \pm 23
P-value			0.0001	0.0351	0.2260	0.7310	0.2807	0.8298	0.9299
Multiple doses	IM	18	119 \pm 34	142 \pm 24	161 \pm 32	155 \pm 33	115 \pm 28	82 \pm 27	33 \pm 15
	IV	13	172 \pm 32	171 \pm 33	162 \pm 35	132 \pm 28	88 \pm 227	63 \pm 23	32 \pm 14
P-value			0.0001	0.0457	0.9322	0.0441	0.0118	0.0630	0.8520

IM = intramuscular. IV = intravenous.

Table 2: Pharmacokinetics of ceftriaxone in the plasma of 39 neonates following intravenous and intramuscular administration. The figures are the mean \pm SD and range, by Mulhall, et al. [45].

	Single dose		P-value	Multiple doses		P-value
	IV (N = 12)	IM (N = 6)		IV (N = 10)	IM (N = 15)	
Cmax ($\mu\text{g/ml}$)	153 \pm 39	141 \pm 19	0.4909	134 \pm 25	143 \pm 23	0.3640
	115 – 236	123 – 175		95 – 179	134 – 212	
Cmin ($\mu\text{g/ml}$)	54 \pm 22	51 \pm 21	0.7856	21.6 \pm 6	25 \pm 5.5	0.0991
	18 - 9 6	25 – 84		13 – 31	18 – 49	
Serum half-life (hours)	15.4 \pm 5.6	15.8 \pm 5.8	0.8894	8.5 \pm 1.5	9.7 \pm 2.2	0.1465
	8.8 – 29	10.6 – 23.4		6.1 – 11.2	6.9 – 16.4	
Clearance (ml/min/kg)	0.28 \pm 0.12	0.28 \pm 0.13	0.9999	0.54 \pm 0.11	0.41 \pm 0.11	0.0082
	0.16 – 0.61	0.15 – 0.40		0.17 – 0.65	0.19 – 0.58	
Distribution volume (ml/kg)	326 \pm 70	323 \pm 38	0.9239	393 \pm 75	321 \pm 52	0.0092
	211 – 434	265 – 376		278 – 527	235 – 401	
Tmax (hours)	---	1.8 \pm 0.8		---	1.4 \pm 0.7	---
	---	0.8 – 3.2		---	0.2 – 2.8	

IM = intramuscular. IV = intravenous. N = number of neonates.

Table 3: Pharmacokinetic parameters of ceftriaxone based on total plasma ceftriaxone concentration at various ages. The figures are the mean \pm SD, by Hayton and Stoeckel [46].

Subjects	N	Half-life (hours)	Distribution volume		Clearance		Fu (%)
			L	L/kg	ml/min	ml/min/kg	
A	24	18.6 \pm 6.9	129 \pm 0.38	0.504 \pm 0.147	0.861 \pm 0.260	0.344 \pm 0.127	72.3 \pm 19.7
B	10	9.7 \pm 3.9	1.79 \pm 0.79	0.650 \pm 0.275	2.48 \pm 1.49	0.934 \pm 0.655	75.2 \pm 20.7
C	11	7.2 \pm 3.2	3.52 \pm 1.52	0.538 \pm 0.248	6.23 \pm 3.2	0.925 \pm 0.400	54.7 \pm 20.0
D	8	6.3 \pm 1.1	4.90 \pm 1.64	0.399 \pm 0.072	9.13 \pm 3.15	0.745 \pm 0.157	60.7 \pm 4.30

A = infants 1-8 days old. B = infants 9-30 days old. C = infants 1-12 months old. D = children 1-6 years old. N = Number of cases. Fu (%) = percent of the dose excreted in urine. Half-life (hours), A versus B, P-value < 0.001, A versus C, P-value < 0.001, A versus D, P-value < 0.001. Distribution volume (L), A versus B, P-value < 0.001, A versus C, P-value < 0.001, A versus D, P-value < 0.001, B versus C, P-value < 0.01, B versus D, P-value < 0.001, C versus D, P-value < 0.05. Distribution volume (L/kg), the groups are not statistically different. Clearance (ml/min), A versus B, P-value > 0.05, A versus C, P-value < 0.001, A versus D, P-value < 0.001, B versus C, P-value < 0.05, B versus D, P-value < 0.001. Clearance (ml/min/kg), A versus B, P-value < 0.001, A versus C, P-value < 0.001, A versus D, P-value < 0.05. Fu (%) the groups are not statistically significant.

Table 4: Susceptibility to ceftriaxone of 4 bacteria recovered from the cerebrospinal fluid cultures of 32 children. The figures are the median, by Del Rio, et al. [47].

Strain	Number of children	Ceftriaxone concentration ($\mu\text{g/ml}$)	
		MIC	MBC
Haemophilus influenzae β -lactamase negative	23	0.001	0.002
Haemophilus influenzae β -lactamase positive	3	0.001	0.002
Neisseria meningitidis	4	0.002	0.002
Streptococcus pneumoniae	2	0.016	0.016

Table 5: Ceftriaxone concentrations ($\mu\text{g/ml}$) in the cerebrospinal fluid measured in 12 infants and children with meningitis. The figures are the range and the mean \pm SD, by Del Rio, et al. [47].

Ceftriaxone dose	Ceftriaxone concentrations ($\mu\text{g/ml}$) in the cerebrospinal fluid of 12 infants and children at indicated time after dose					
	0.5 hours	1 hour	2 hours	4 hours	6 hours	12 hours
Single dose (50 mg/kg)	0.26 - 3.3 2.1 \pm 1.6	1.2 - 3.0 2.2 \pm 0.08	3.2 3.2 \pm 0	11.4 - 4.3 2.5 \pm 1.2	2.8 - 7.2 4.2 \pm 2.1	---
Multiple doses						
Dose 1 (75 mg/kg)	1.8, 3.7	4.2	1.2, 6.0	3.6, 4.3	7.2	1.8, 4.4
Last dose (50 mg/kg)	5.2, 10.4	5.2	3.0, 8.85	1.45, 4.8	4.8	0.94, 2.4

Range and mean \pm SD provided when three or more samples were analyzed.

concentrations ranged from 145 to 400 µg/ml (mean ± SD = 230 ± 70.2 µg/ml) after the first dose, and from 150 to 410 µg/ml (mean ± SD = 263 ± 79.8 µg/ml), after the last dose.

Chadwick, et al. [48] measured the percent concentration of ceftriaxone in cerebrospinal fluid to plasma ratio after ceftriaxone single doses of 75 mg/kg and 50 mg/kg to infants and children. The mean ± SD of the percent penetration into the cerebrospinal fluid to plasma ratio was 4.4 ± 2.8 in 8 infants and children 3.0 ± 1.1 hours after ceftriaxone administration of 75 mg/kg, and 4.8 ± 4.6 in 8 infants and children at a mean ± SD of 2.8 ± 1.0 hours after 50 mg/kg ceftriaxone administration.

Bacterial resistance to ceftriaxone in infants and children:

Out of 208 blood samples, 19.2% had positive blood culture [49]. Single C-reactive protein had sensitivity and specificity of 87.5% and 70.9%, respectively, while Rubarth's newborn scale sepsis had sensitivity of 65% and specificity of 79.7%. Isolated bacteria were *Klebsiella* species, (35%), *Escherichia coli* (22.5%), Coagulase negative staphylococci (30%), *Staphylococcus aureus* (10%), and *Pseudomonas* species (2.5%). The resistance to ceftriaxone was 45%.

Falup-Pecurariu, et al. [50] reported high colonization rates among 400 healthy infants and children, and moderate (66%) coverage by PCV7 and PCV10, with a superior (80%) PCV13 coverage. Most frequent serotypes were 23F, 6B, 19F, and 14, resistance to ceftriaxone was 18%, and 67% isolates were multidrug resistant.

Shi, et al. [51] reported the serotype distribution, antibiotic resistance pattern and multilocus sequence types of 111 invasive pneumococcal disease strains isolated from children < 14 years old. The most common serotypes of invasive pneumococcal disease were 19F, 19A, 14, 23F, and 6B, and the PCV13 coverage rate was 90.1%. For the meningitis isolates, the non-susceptibility to ceftriaxone was 65.2%, and the multidrug resistance rate of all isolates was 89.2%. The most common sequence types were ST320, ST271, and ST876. And ST81, which belonged to serotype 14A, 19F, 14, and 23F, respectively.

A total of 61 children aged < 5 years had confirmed invasive pneumococcal disease [52]. The serotype distribution of those isolates were 19A (41%), 14 (19.7%), 19F, (11.5%), 23F (9.8%), 8 (4.9%), 9V (4.9%), 1 (3.3%), and 4, 6B, and 20 (each 1.6%). The percentage of *Streptococcus pneumoniae* strains resistant to ceftriaxone was 18.0%, and the multidrug-resistant strains were 95.6%.

Nasopharyngeal swabs were collected on admission from 85 children who had not received antimicrobials for their admission illness [53]. The overall prevalence of nasopharyngeal *Streptococcus pneumoniae* was 44%. Carriage occurred more often in Aboriginal children from rural areas (56%) than in urban children (24%) (*P*-value < 0.01). Thirty-five percent were ceftriaxone resistant.

Skull, et al. [54] conducted a prospective cohort study in 250 children. *Streptococcus pneumoniae* was detected in 52%

(1,028/1,974) of all nasopharyngeal swabs. *Streptococcus pneumoniae* was isolated from 92% of children at some time. Ceftriaxone resistance was found in 19% of children's first isolates.

A total of 794 children aged 1 to 60 months were enrolled [55]. The pneumococcal detection rate was 21%, being higher among children who had not received PCV13 vaccination, lived in rural areas, had an enclosed kitchen, were malnourished or presented with fever (*P*-value < 0.05). The predominant serotypes were 19F, 11, 6A/B/C/D and 10A. A percentage of 37 was not susceptible to ceftriaxone.

Ceftriaxone is the drug of choice for typhoid fever and the emergence of resistant *Salmonella Typhi* raises major concerns for treatment [56]. A plasmid belonging to incompatibility group 11 (Incl-ST31) which included blaCTX-M-15 (ceftriaxone resistance) associated with ISEcp-1 was identified. High similarity (90%) was seen with pS115, an Incl1 plasmid from *Salmonella Enteritidis*, and with pESBL-EA11, an incl1 plasmid from *Escherichia coli* (99%) showing that *Salmonella Typhi* has access to ceftriaxone resistance through the acquisition of common plasmids.

Shigella infection is one of the major causes of diarrhoea worldwide, and especially in developing countries. Antimicrobial resistance has complicated the empirical treatment. Nikfar, et al. [57] defined the clinical and antibiotic resistance patterns of *Shigella* gastroenteritis cases. Among 193 *Shigella* isolates, *Shigella flexneri* (64.8%) was the predominant species followed by *Shigella sonnei* (32.6%). The resistance to ceftriaxone was 51%. Due to the high resistance to ceftriaxone, this drug is not recommended as an empirical therapy for shigellosis.

The enteric pathogens causing diarrhoea impair children's health severity. Zhang, et al. [58] retrospectively analyzed 1,577 pathogens isolated from inpatients and outpatients. *Salmonella* presented the highest frequency (36.0%), followed by diarrheagenic *Escherichia coli* (23.7%), *Staphylococcus aureus* (15%), *Shigella* (13.1%), and *Aeromonas* (4.6%). The highest proportion of all enteric pathogens was found in infants (67.6%). *Shigella* was more resistant to ceftriaxone than *Salmonella*, and the multidrug resistance was 58.2% of *Shigella* and 45.9% of *Salmonella*.

Chiappini, et al. [59] investigated the resistance rates and their modifications among *Salmonella* enteric strains isolated from Italian children aged > 5 years hospitalized for acute diarrhoea. *Salmonella* enteric strains were isolated from stool cultures. A total of 2,003 children aged 1 month to 16.8 years (median age 10.3 years) with acute diarrhoea were enrolled. *Salmonella* enteric strains were isolated from 218 (10.9%) children. A total of 148 (67.9%) isolates were resistant to at least 1 antibiotic and 57 (26.1%) children were multidrug resistant. The resistance to ceftriaxone was 1.8%.

Tamma, et al. [60] conducted a retrospective study to compare clinical outcomes between children treated with ceftriaxone. There were a total of 783 unique children with

Enterobacteriaceae. Seventy-six (9.7%) children had clinical isolates resistant to ceftriaxone.

Peco-Antic, et al. [61] assessed the resistance patterns of uropathogens in newborns and young children with acute pyelonephritis. A total of 117 newborns and 294 children aged 6.3 ± 0.7 months were treated during early ($N = 117$) or late ($N = 275$) study period due to the first episode of acute pyelonephritis. *Escherichia coli* was the most common bacterial pathogen (85.5%), and the multidrug resistance was more common in newborns during the early study period.

Bujdakova, et al. [62] assessed the occurrence and transferability of β -lactam resistance in 30 multidrug-resistant *Escherichia coli*, *Klebsiella* species, *Pantoea agglomerans*, *Citrobacter freundii*, and *Serratia marcescens* strains isolated from children aged 0 to 3 years. These bacteria were resistance to ceftriaxone for 30%. Twenty-eight of 30 isolates possessed a transferable resistance confirmed by conjugation and isolation of 79-89-kb plasmids. The β -lactam resistance was due to production of β -lactamases and ceftazidime proved to be stronger β -lactamase inductor than ceftriaxone.

Enteroaggregative *Escherichia coli* has been implicated as an emerging cause of traveller's diarrhoea, persistent diarrhoea among children, and immunocompromised patients. Overall, 28.1% of the isolates were positive for at least one of virulence genes [63]. The most frequent gene was *aap* with a frequency of 96.9%. Neither *aafA* nor *aggA* genes were detected among Enteroaggregative *Escherichia coli* isolates. Antimicrobial susceptibility testing revealed 81.3% resistant to ceftriaxone. Further analysis revealed that the rate of extended-spectrum β -lactamases-producing isolates was 71.9%. PCR screening revealed that 87.5% and 65.5% of Enteroaggregative *Escherichia coli* isolates were positive for *bla*_{TEM} and *bla*_{CTX-M} genes, respectively.

A total of 89,643 paediatric blood cultures were performed and 10,621 pathogens were included in the analysis [64]. Estimated minimum incidence rates of bloodstream infections for children aged ≤ 5 years fell from a peak of 11.4 per 1,000 persons in 2002 to 3.4 per 1,000 persons in 2017. Over two decades, resistance to all empiric first-line antimicrobials, including ceftriaxone among children aged ≤ 5 years increased from 3.4% to 30.2% (P -value < 0.001). *Klebsiella* species resistance to all first-line antimicrobial regimens, including ceftriaxone, increased from 5.9% to 93.7% (P -value < 0.001). The incidence of bloodstream infections among hospitalized children has decreased substantially over the last 20 years, although gains have been offset by increasing in gram-negative pathogens resistant to all empiric first-line antimicrobials.

Discussion

Ceftriaxone is a versatile and useful third-generation β -lactam-resistant cephalosporin. It is given intravenously or intramuscularly once a day. This antibiotic is active against gram-positive and gram-negative bacteria [1]. Ceftriaxone is used to treat sepsis and disseminated gonococcal infection and meningitis caused by *Escherichia coli*, *Klebsiella*,

Proteus, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Citrobacter*, *Serratia*, *Neisseria gonorrhoea*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Bacteroides* species [2]. Ceftriaxone distributes widely in body tissues and in body fluids and penetrates into the cerebrospinal fluid at significant concentration and it is used to treat bacterial meningitis [3]. After the administration of 75 mg/kg ceftriaxone, the cerebrospinal fluid ceftriaxone concentration range from 0.7 to 8.3 $\mu\text{g/ml}$ three hours after the administration [4]. Congeni et al. [5] administered a ceftriaxone loading dose of 100 mg/kg, followed by a single daily dose of 80 mg/kg to 57 infants and children. Pathogens included *Haemophilus influenzae*, *Neisseria meningitis*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*. All patients showed clinical improvement and all were bacteriologically cured. Thirty-four patients aged 1 month to 19 years with suspected bacterial meningitis were treated with ceftriaxone. The overall bacteria cure was 88%, with a clinical response of 96%. Ceftriaxone is a safe and effective antibiotic and is used in the treatment of serious infections in infants and children [6]. Swann et al. [7] and Craig et al. [8] treated infants and children suffering from bacterial meningitis with a single daily dose of 100 mg/kg ceftriaxone for seven days. All patients were cured; ceftriaxone is an effective, safe and well tolerated antimicrobial agent for the treatment of childhood meningitis. *Streptococcus pneumoniae* was isolated from the cerebrospinal fluid of children with meningitis; ceftriaxone cured all children [9]. A total of 119 infants and children aged 3 weeks to 15.5 years, with acute bacterial meningitis, were treated with ceftriaxone 100 mg/kg on days one and two and 60 mg/kg thereafter for 4 to 6 days (short course) or 8 to 14 days (full course). Complete clinical recovery was noted in 88% of patients [10]. A single daily dose of 100 mg/kg ceftriaxone for 13 days is effective in the treatment of meningitis caused by *Haemophilus influenzae* type b, *Neisseria meningitis*, *Streptococcus pneumoniae*, group B streptococcus, *Streptococcus viridians*, and *Staphylococcus epidermidis* [11]. A single daily dose of 100 mg/kg ceftriaxone for days one and two was followed by 60 mg/kg thereafter. The short course (4 to 7 days) was compared with standard-treatment course twice as long. The short-course regimen was adequate for the treatment of bacterial meningitis [12]. The efficacy of parenteral ceftriaxone administration for the treatment of purulent meningitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, or *Neisseria meningitis* was compared 5 to 10 days of administration [14]. In the 5-day group, two children had a relapse; there were no relapses in the 10-day group. After a single daily dose of 50 mg/kg ceftriaxone, microbiologic cure was achieved in 91% infections and the clinical cure occurred in 96% [15].

Ceftriaxone is effective in the treatment of nasopharyngeal bacteria flora [16, 17], gonococcal ophthalmia [18] and epiglottitis [19] in infants and children. Ceftriaxone has biliary [21 - 27], renal [28 - 31], and haemolytic [32 - 37] adverse events. Ceftriaxone displays bilirubin from albumin binding sites [30, 39], thereby increases the amount of free unconjugated bilirubin. Ceftriaxone should not be used in neonates at risk of

developing unconjugated hyperbilirubinaemia. The concurred administration of ceftriaxone and calcium-containing solution or products in neonates and infants is contraindicated [40 - 43].

Ceftriaxone extensively binds to plasma proteins [44]. This drug slowly decays from neonatal plasma. After an intravenous dose of 50 mg/kg ceftriaxone to neonates, the mean ceftriaxone plasma concentrations were 155, 147, and 110 µg/ml 0.25, 1, and 7 hours, respectively, after dosing [45]. At 0.25 and 0.5 hours after ceftriaxone, the plasma concentrations of this antibiotic were significantly higher after intravenous than intramuscular administration [Mulhall et al. 1985]. In neonates, the pharmacokinetic parameters of ceftriaxone are not different after intravenous and intramuscular administration [45]. The mean half-lives (hours) of ceftriaxone are 18.6, 9.7, 7.2, and 6.3 in infants 1-8 days old, 9-30 days old, 1-12 months old, and in children 1-6 years old, respectively [46].

Some bacteria may become resistant to ceftriaxone. Resistance to ceftriaxone was observed for *Klebsiella* species, *Escherichia coli*, Coagulase negative staphylococci, *Staphylococcus aureus*, and *Pseudomonas* species [49]. *Streptococcus pneumoniae* may become resistant to ceftriaxone [51 - 55]. *Salmonella Typhi* [56], and *Shigella* [57 - 58] may become resistant to ceftriaxone. *Salmonella* [59] Enterobacteriaceae [60], *Escherichia coli* [61 - 63], and *Klebsiella* species [62] were found to be resistant to ceftriaxone at various percentages of resistance.

In conclusion, ceftriaxone is a β -lactam-resistant third-generation cephalosporin. It is active against some important gram-positive and most gram-negative bacteria. Ceftriaxone is active against *Escherichia coli*, *Klebsiella*, *Proteus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Citrobacter*, *Enterobacter*, *Serratia*, *Neisseria gonorrhoea*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Bacteroides* species. This antibiotic may be administered intravenously or intramuscularly once a day to treat bacterial meningitis. Ceftriaxone widely distributes in body tissues and in body fluids and penetrates into the cerebrospinal fluid at significant extent, thus is used to treat bacterial meningitis. The dose of ceftriaxone is 50 or 100 mg/kg per day in infants and children. A single intravenous daily dose of ceftriaxone of 100 mg/kg, for 7 or 13 days, is effective in the treatment of bacterial meningitis. Ceftriaxone is used to treat nasopharyngeal bacterial infection, gonococcal ophthalmia, and epiglottitis. Ceftriaxone may cause biliary, renal, and haemolytic adverse events. This antibiotic displays bilirubin from albumin binding sites and should not be administered to infants that are at risk of hyperbilirubinaemia. Concurred administration of calcium and ceftriaxone is contraindicated. Ceftriaxone extensively binds to plasma proteins, and the concentration of this antimicrobial slowly decays from neonatal plasma. Ceftriaxone half-life is age-dependent and is longer in infants than in children. Some bacteria may become resistant to ceftriaxone.

Conflict of interests

The author declares no conflicts of financial interest in any

product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

This article is a review and drugs have not been administered to men or animals.

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