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Journal of Pharmaceutics and Pharmacology Research
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Research Article

Clinical Pharmacology of Ceftriaxone

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Received date: August 25, 2023; Accepted date: September 12, 2023; Published date: September 27, 2023

Citation Gian Maria Pacifici, (2023), Clinical Pharmacology of Ceftriaxone, *J. Pharmaceutics and Pharmacology Research*, 6(5); **DOI: 10.31579/269-7247/145**

Abstract

Ceftriaxone is a third-generation cephalosporin and is resistant to many narrow-spectrum β-lactamases and has good activity against most gram-positive and gram-negative aerobic bacteria. Ceftriaxone is the drug of choice for treatment of serious infections caused by Escherichia coli, Klebsiella, Proteus, Haemophilus influenzae, Moraxella catarrhalis, Citrobacter, Enterobacter, Serratia, Neisseria gonorrhoea, Staphylococcus aureus, Streptococcus pneumoniae, and Streptococcus pyogenes, and for severe forms of Lyme disease. Ceftriaxone treats ureteral, cervical, rectal, and pharyngeal infection, gonorrhoea, Lyme disease, and bacterial meningitis. The efficacy and safely of ceftriaxone have been reviewed. Following intravenous administration, ceftriaxone rapidly diffuses into the body with a distribution half-life of about 14 min. A half of ceftriaxone is eliminated by renal route and the remainder is secreted into the bile. The elimination half-life of ceftriaxone is 6.4 hours in patients with normal renal function and 21.4 hours in patients with renal failure. The prophylaxis, treatment, and trials with ceftriaxone have been reviewed. Ceftriaxone penetrates into the cerebrospinal fluid in significant amounts, treats bacterial meningitis, some bacteria may become resistant to ceftriaxone, and ceftriaxone is poorly transferred across the human placenta, and poorly migrates into the breast-milk. The aim of this study is to review ceftriaxone efficacy and safely, pharmacokinetics, prophylaxis, treatment, trials, penetration into the cerebrospinal fluid, treatment of bacterial meningitis, resistance to bacteria, transfer across the human placenta, and migration into the breast-milk.

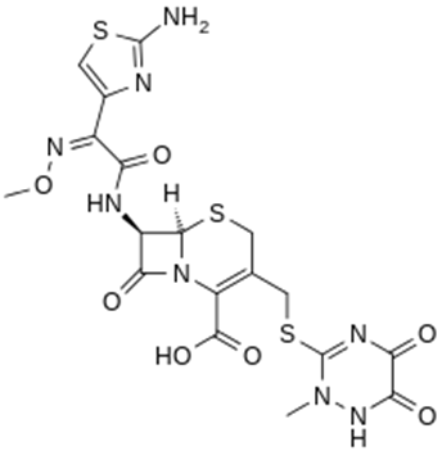
Key words: breast-milk; ceftriaxone; cerebrospinal-fluid; efficacy-safely; meningitis; pharmacokinetics; placental-transfer;prophylaxisresistance;treatment;trials

Introduction

Pharmacology of ceftriaxone Ceftriaxone is a third-generation cephalosporin is resistant to many narrow-spectrum β-lactamases and has good activity against most gram-positive and gram-negative aerobic bacteria. Ceftriaxone activity is very similar to that of cefotaxime but a longer elimination half-life of 8 hours allowing for only-daily dosing for most indications. Administration of the drug twice-daily has been effective for patients with meningitis. About half of the drug can be recovered from the urine; the remainder is eliminated by biliary secretion. Single doses of intramuscular ceftriaxone have long been used in the management of ureteral, cervical, rectal, or pharyngeal gonorrhoea; increasing resistance has necessitated the use of higher doses (recently increased to 500 mg) [1].

Antimicrobial spectrum of ceftriaxone

Ceftriaxone is the drug of choice for treatment of serious infections caused by Escherichia coli, Klebsiella, Proteus, Haemophilus influenzae, Moraxella catarrhalis, Citrobacter, Enterobacter, Serratia, Neisseria gonorrhoea, Staphylococcus aureus, Streptococcus pneumoniae, and Streptococcus pyogenes, and for severe forms of Lyme disease. Ceftriaxone is used for the empiric treatment of meningitis in non-immunocompromised adults and children (in combination with vancomycin and ampicillin pending identification of the causative agent), owing to its excellent activity against to Haemophilus influenzae, sensitive Streptococcus pneumoniae, Neisseria meningitides, and gram-negative enteric bacteria. Ceftriaxone lacks activity against Listeria monocytogenes and penicillin-resistant pneumococci, which may cause meningitis. The antimicrobial spectrum of ceftriaxone is excellent for the treatment of community-acquired pneumonia [1].



Ceftriaxone molecular structure (molecular weight = 554.58 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "ceftriaxone efficacy, safely", "ceftriaxone pharmacokinetics", "ceftriaxone prophylaxis" "ceftriaxone treatment", "ceftriaxone trials", ceftriaxone CSF", "ceftriaxone meningitis", "ceftriaxone resistance", "ceftriaxone placental transfer", and "ceftriaxone breast-milk". In addition, the book "The pharmacological basis of therapeutics" [1] has been consulted.

Results

Efficacy and safely of ceftriaxone

Ceftriaxone administered intravenously at a dose of 2 grams twice-daily effectively and safely treats patients with community-acquired pneumonia [2,3]. Ertapenem and ceftriaxone administered intravenously at a dose of 1 gram once-daily have similar efficacy and safely in treatment of hospitalized patients with community-acquired pneumonia [4]. Ceftriaxone administered intravenously at a daily dose of 2 or 4 grams effectively and safely treats patients with amyotrophic lateral sclerosis [5]. ceftriaxone administered intravenously at a daily dose of 250 mg effectively and safely treats patients with uncomplicated gonorrhoea [6]. ceftriaxone administered intravenously at a daily dose of 2 gram effectively and safely treats paediatric patients with urinary-tract, lower respiratory-tract, skin, soft-tissue, bone and joint infections, bacteraemia, and septicaemia caused by gram-negative bacteria [7]. treats serious infections caused by gram-negative bacteria in paediatric patients [8], and ceftriaxone administered intravenously at a dose of 50 to 80 mg/kg once-daily effectively and safely paediatric patients infected by Haemophilus influenzae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, or by Escherichia coli [9].

Pharmacokinetics of ceftriaxone in patients with severe sepsis

Joynt et al. [10]. studied the pharmacokinetics of ceftriaxone in 12 patients with nosocomial pneumonia, intraabdominal sepsis, or urinary sepsis and ceftriaxone was intravenously infused at a dose of 2 grams once-daily. The patients were aged 45±16 years (range, 33 to 68) weighed 62±13 kg (range, 52 to 96), had a creatinine serum concentration of 70.7±24.2 µmol/L (range, 41 to 111), a creatinine clearance of 97.7±49.6 ml/min (range, 21 to 167), an album in concentration of 22.2±6.1 grams/L (range, 19 to 31) and a bilirubin concentration of 39.6±50 µmol/L (range, 9 to 155). Ten patients had normal renal function and 2 patients had renal failure.

Table 1. Pharmacokinetic parameters of ceftriaxone which have been obtained in 12 patients with nosocomial pneumonia, intraabdominal sepsis, or urinary sepsis. Ten patients had normal renal function and 2 patients had renal failure. Values are the minimum, maximum, mean, and±SD, by

										Trough conc. (µg/ml) [a]	
Value	Vc (L)	Vss (L)	K_{el} (min^{-1})	K_{12} (min^{-1})	K_{21} (min^{-1})	$T_{1/2}\alpha$ (min)	$T_{1/2}\beta$ (h)	TBC (ml/min)	Peak conc. (µg/ml)	Day 1	Day 3
Ten patients with normal renal function											
Minimum	1.3	13.6	0.00022	0.013	0.012	6.0	4.8	23.0	148	< 5	< 5
Maximum	7.2	22.6	0.0108	0.085	0.026	26.0	7.2	62.0	242	14.0	13.0
Mean	5.9	19.9	0.0072	0.042	0.017	13.3	6.4	41.3	205	8.8	9.6
±SD	1.3	3.3	0.0022	0.023	0.008	6.8	1.1	11.7	31.3	3.0	7.2
Two patients with renal failure											
Patient 4	7.0	25.7	0.0031	0.022	0.008	21.0	14.5	22.0	205	21.0	25.0
Patient 11	6.5	41.2	0.0027	0.038	0.007	15.0	28.4	18.0	184	27.0	49.0
Mean	6.8	33.5	0.0029	0.030	0.008	18.0	21.4	19.9	194	24.2	36.9
±SD	0.3	11.0	0.0003	0.011	0.001	4.7	9.8	3.1	15.0	4.0	17.1
All patients (N = 12)											
Mean	6.0	22.4	0.0064	0.041	0.015	14.0	9.2	37.0	203	12.0	16.0
+SD	1.2	7.1	0.0026	0.022	0.008	7.0	6.9	14.0	29.0	7.0	14.0

Vc = distribution volume of the central compartment. Vss = distribution volume at steady-state. K_{el} = elimination-rate constant. K_{12}, K_{21} = rate constant between the two compartments. $T_{1/2}\alpha$ = distribution half-life. $T_{1/2}\beta$ = elimination half-life. TBC = total body clearance. Peak conc. = peak concentration. [a]Trough concentration of ceftriaxone measured at day 1 and at day 3 of treatment.

This table shows that ceftriaxone rapidly distributes into the body with a mean distribution half-life is 14 min and is slowly eliminated with a mean elimination half-life is 9.2 hours in all patients. The comparison of the pharmacokinetic parameters of ceftriaxone obtained in patients with normal renal function to those obtained in patients with renal failure is difficult because the small number of patients with renal failure however the impression prevails that the pharmacokinetic parameters of ceftriaxone are different in these two groups of patients. In particular, the mean elimination half-life of ceftriaxone is 6.4 hours in patients with normal renal function and 21.4 hours in patients with renal failure. Ceftriaxone is largely eliminated by renal route thus the renal function is an important factor for the clearance of ceftriaxone from the body. Joynt et al. [10] stated that that moderate or severe renal failure causes approximately three-fold increase in the elimination half-life, a 50% increase in the distribution volume at steady-state, and halved the total body clearance. There is remarkable inter-patient variability in the pharmacokinetic parameters of ceftriaxone and this variability is accounted by the wide variability in patient's demographic characteristics and disease.

Prophylaxis with ceftriaxone

Ceftriaxone administered intravenously at a daily dose of 2 grams prevents both local and remote postoperative infections more effectively (P-value = 0.01) than other antibiotics [11], intravenous ceftriaxone plus intravenous metronidazole prevents the infection in children with perforated appendicitis more effectively than anti-pseudomonal antibiotics [12]. ceftriaxone administered intravenously at a daily dose of 1 gram is more effective than norfloxacin administered orally at the dose of 400 mg twice-daily (P-value = 0.03) for the prophylaxis of bacterial infections in patients undergoing surgery [13], one single intravenous dose of 1 gram of ceftriaxone is effective as ampicillin/cloxacillin administered intravenously at a dose of 1 gram 3 times-daily in preventing complications during post-Caesarean section [14]. intravenous ceftriaxone prevents surgical infections, urinary-tract infections, and respiratory-tract infections more effectively (P-value < 0.04) than another cephalosporin such as cefamandole, cefazolin, cefotaxime, cefoxitin or cefuroxime [15] and ceftriaxone administered intravenously at a daily dose of 2 grams prevents infection in patients undergoing colorectal surgery more effectively (P-value < 0.001) than penicillins [16]. a single intravenous dose of 2 grams of ceftriaxone administered intravenously at the induction of anaesthesia prevents the infection in patients undergoing orthopaedic surgery [17]. ceftriaxone administered intravenously at a single dose of 2 grams before surgery and administered at an intravenous dose of 2 grams for 2 days after surgery prevents the infection in patients undergoing liver transplantation [18], ceftriaxone administered at an intragluteal daily dose of 2 grams prevents the infection in patients undergoing orthopaedic and traumatic surgery [19].ceftriaxone administered intravenously at a daily dose of 2 grams prevents post-operative pyrexia and infections in patients undergoing chest surgery and shorts the hospital stay [20].and ceftriaxone administered intravenously at a daily dose of 2 grams is more efficacious than placebo (P-value = 0.001) for the prevention of infections in patients undergoing chest surgery [21].

Treatment of bacterial infection with ceftriaxone

Intravenous ceftriaxone has similar efficacy as intravenous benzylpenicillin in treating patients with neurosyphilis [22]. ceftriaxone administered intravenously at a dose of 2 grams once-daily treats endocarditis, spondylodiscitis, and prosthetic joint infections caused by Cutibacterium acnes [23]. ceftriaxone administered intravenously at a daily dose of 1 or 2 grams for 3 to 6 days treats patients with uncomplicated and severe forms of leptospirosis [24]. ceftriaxone administered intravenously at a daily dose of 2 grams treats patients with acute tonsillopharyngitis [25]. a single intravenous dose of 2 grams of ceftriaxone treats patients with meningococcal meningitis [26]. ceftriaxone administered intravenously at a daily dose of 3 grams for 7 days treats patients with typhoid fever [27]. ceftriaxone administered intravenously once-daily at a dose of 2 grams for 4 weeks treats patients with streptococcal endocarditis [28]. ceftriaxone administered intramuscularly at a dose of 1 gram 4 times-daily every 2 days treats patients with primary and secondary syphilis [29]. intramuscular ceftriaxone has been found efficacy as intravenous trimethoprim-sulfamethoxazole in the treatment of patients with urinary-tract infections [30]. ceftriaxone administered intravenously at a dose of 2 grams once-daily for 14 days treats patients with acute disseminated Borrelia burgdorferi infection as doxycycline administered orally at a dose of 100 mg twice-daily for 21 days [31]. ceftriaxone administered intravenously at a dose of 1 gram twice-daily treats patients with respiratory-tract, urinary-tract, skin, soft-tissue, bone and joint infections, catheter-related septicaemia, liver abscess, and otitis media [32]. ceftriaxone administered intravenously at a dose of 1 gram once-daily treats patients with bacteriologically proven cellulitis, suppurative diabetic foot ulcer, and soft-tissue infections [33]. ceftriaxone administered intravenously at a dose of 1 gram twice-daily effectively treats patients with respiratory-tract, urinary-tract, skin, soft-tissue, bone, and joint infections caused by Staphylococcus aureus, aerobic gram-positive cocci, Enterobacteriaceae, or by Pseudomonas aeruginosa [34]. and ceftriaxone administered intravenously at a dose of 1 gram twice-daily treats patients with skin, soft-tissue, urinary-tract, biliary-tract infections, pneumonia, and sinusitis caused by Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus faecalis, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Serratia marcescens, Enterobacter cloacae, Haemophilus influenzae, Pseudomonas aeruginosa, Bacteroides fragilis, or by anaerobic cocci [35].

Trials with ceftriaxone

Ceftriaxone administered intravenously at a dose of 2 grams twice-daily for 3 days is more effective than placebo in treating gallbladder infection and diarrhoea caused by Clostridium difficile in adult patients [36]. ceftriaxone administered intravenously at a dose of 2 grams once-daily is effective as multiple dosing regimens of anti-staphylococcal antibiotics in treating patients infected by methicillin-susceptible Staphylococcus aureus [37]. ceftriaxone administered intravenously at a daily dose of 1 gram is effective as ceftriaxone administered intravenously at a daily dose of 2 grams in treatment of adult patients with community-acquired pneumoniae [38]. a 12-month follow-up resulted that ceftriaxone administered intravenously at a daily dose of 1 gram treats early syphilis as doxycycline, or tetracycline, or penicillin administered intravenously at a daily of 1 gram [39]. ertapenem administered intravenously at a dose of 1 gram once-daily for 3 days is efficacy as ceftriaxone administered intravenously at a dose of 2 grams once-daily for 3 days in treatment of acute pyelonephritis in adult patients [40]. ceftriaxone administered intravenously at a dose of 2 grams once-daily for 3 days is efficacy as cefditoren pivoxil administered orally at a dose of 400 mg once-daily for 3 days in treatment of acute pyelonephritis in adult patients [41]. ceftriazone administered intravenously at a daily dose of 2 grams is 3 times more effective than ampicillin/sulbactam administered intravenously at a daily dose of 3 grams in treatment of postoperative neurosurgical infections in adult patients [42].and ceftriaxone administered intravenously at a daily dose of 2 grams is efficacy as cefotaxime administered intravenously at a dose of 2 grams 4 times-daily in treatment of serious bacterial infections [43].

Penetration of ceftriaxone into the cerebrospinal fluid (CSF)

Nau et al. [44]. investigated the penetration of ceftriaxone into CSF of 7 patients with uninflamed meninges aged 59.7±3.3 years (range, 49 to 76) and weighing 78.6±3.0 kg (range, 65 to 90). All patients had respiratory-tract infection, 2 patients had intracerebral blending, and 2 patients had

cerebral ischemic infarction. Ceftriaxone was intravenously infused at a dose of 2 grams twice-daily for 3 days. Table 2 summarizes the pharmacokinetic parameters of ceftriaxone in CSF.

Table 2. Pharmacokinetic parameters of ceftriaxone which have been obtained in CSF of 7 patients. Ceftriaxone was intravenously infused at a dose of 2 grams twice-daily for 3 days. Values are the minimum, maximum, mean, and ±SD, by Nau et al. [44].

	Results obtained after the 1st dose					Results obtained after the 3rd dose	
Value	Peak Conc. (µg/ml)	Tmax (h)	$AUC_{0-\infty}$ (µg*h/ml) in CSF	$AUC_{0-\infty}$ (µg*h/ml) in serum	§$AUC_{0-\infty}$ CSF/serum	[a]Conc. (µg/ml)	*Half-life (h)
Minimum	0.18	1.00	2.30	896	0.0025	0.30	15.7
Maximum	1.04	16.0	18.1	2,406	0.0075	1.03	18.4
Mean	0.53	11.4	9.00	1,174	0.0076	0.62	17.0
±SD	0.15	2.70	2.82	964	0.0040	0.21	0.78

Tmax = time to reach the peak concentration in CSF. $AUC_{0-\infty}$ = area under concentration-time curve from 0 to infinity. §$AUC_{0-\infty}$ = ratio of the area under the concentration-time curve in CSF to that in serum. [a]Concentration of ceftriaxone in CSF which has been measured 12 hours after the end of the 3rd infusion. *Elimination half-life.

This table shows that the peak concentration of ceftriaxone in CSF exceeds the minimum inhibitory concentration of Neisseria meningitides, Haemophilus influenzae, penicillin G-sensitive Streptococcus pneumoniae, Borrelia burgdorferi, and some members of the family of Enterobacteriaceae by approximately 10-fold thus ceftriaxone is bactericidal. Ceftriaxone slowly penetrates into CSF as the mean time to reach the peak concentration is 11.4 hours. The ratio of the mean area under the concentration-time curve in CSF to that in serum is 0.0076 suggesting that ceftriaxone resides mainly in serum. Ceftriaxone is slowly eliminated from CSF as the mean elimination half-life is 17.0 hours. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters of ceftriaxone in plasma and in CSF and this variability is accounted by the wide variation in patient's demographic characteristics and disease [44]. Ceftriaxone was administered intravenously at a median daily dose of 6.5 grams (range, 4 to 9) corresponding to a median daily dose of 97.5 mg/kg (range, 77 to 131) to 16 patients with meningitis caused by Streptococcus pneumoniae which had a minimum inhibitory concentration of 0.5 µg/ml. The median concentration of ceftriaxone in CSF is 13.3 µg/ml (range, 0.9 to 91.2) thus the concentration of ceftriaxone in CSF is higher than the minimum inhibitory concentration of Streptococcus pneumoniae and ceftriaxone treats the meningitis caused by this organism [45]. Ceftriaxone was intravenously infused at a daily dose of 50 or 75 mg/kg to 17 paediatric patients, aged 0.6 to 52 months, with meningitis caused by Haemophilus influenzae. The mean peak concentration of ceftriaxone in plasma is 267 and 184 µg/ml following the administration of ceftriaxone at the daily dose of 75 and 50 mg/kg, respectively. The mean peak concentration of ceftriaxone in CSF exceeds the minimal inhibitory concentrations of Haemophilus influenzae by 480 to 5,600-times, the mean elimination half-life of ceftriaxone in CSF is 4.2 hours, and the mean penetration-rate of ceftriaxone into CSF is 4.8±3.5% thus ceftriaxone is an appropriate antibiotic to treat the meningitis caused by Haemophilus influenzae in paediatric patients [46].

Treatment of bacterial meningitis with ceftriaxone

Ceftriaxone was administered intravenously at a daily dose of 100 mg/kg on day one followed by a daily dose 80 mg/kg to 14 patients with the meningitis caused by Haemophilus influenzae type b, to 5 patients with the meningitis caused by Streptococcus pneumoniae and to 3 patients with the meningitis caused by Neisseria meningitides. The concentration of ceftriaxone in the cerebral spinal fluid is 10 to 100-fold higher the minimum inhibitory concentration of the pathogens causing the meningitis 24 hours after starting the treatment and is 5 to 50-fold higher the minimum inhibitory concentration of the organisms causing the meningitis at the end of therapy. Thus, ceftriaxone is an effective antibiotic for treatment of bacterial meningitis [47]. A single intravenous dose of 50 mg/kg of ceftriaxone was administered to adult patients with the meningitis caused by Neisseria meningitides (N = 34), Streptococcus pneumoniae (N = 25), Escherichia coli (N = 25), Klebsiella pneumoniae (N = 3), Haemophilus influenzae (N = 2), Viridians streptococci (N = 2), or by unknown organism (N = 16). The mean trough concentration of ceftriaxone in the cerebral spinal fluid is 3.5 µg/ml and the mean trough bactericidal titre is 1:128 thus a single dose of 50 mg/kg of ceftriaxone treats the meningitis caused by different bacteria [48]. Ceftriaxone was administered intravenously at a dose of 100 mg/kg once-daily to 53 infants and children and was administered intravenously at a dose of 60 mg/kg 4 times-daily to 53 infants and children. Subjects were aged 3 years (range, 42 days to 16 years) and the meningitis was caused by Haemophilus influenzae. The cerebral spinal fluid becomes sterilized 18 to 36 hours after the start of treatment, the clinical response is similar according the two treatments, and the meningitis is cured in all children [49].

Resistance of bacteria to ceftriaxone

Strains of non-typhoid Salmonella were isolated from 50 children and the isolates had an increased resistance to ceftriaxone. The dissemination of extended-spectrum-β-lactamase-producing Salmonella isolates results in an increased prevalence of ceftriaxone resistance in children. The resistance of this organism to ceftriaxone is increasing and constitutes a serious problem in children [50]. Multiple prescriptions of ceftriaxone and ceftriaxone misuse induce resistance to ceftriaxone in isolates of non-typhoid Salmonella. Ceftriaxone-resistant in non-typhoid Salmonella infection is increasing problem and limits treatment options for serious infections caused by this bacterium [51]. Salmonella producing β-lactamases has spread rapidly worldwide and poses a serious problem to human health. The resistance of this organism to ceftriaxone is found in 33.6% of isolates and the resistance genes are blaCTX-M, blaTEM, and blaOXA which are detected in 207 (94.1%), 99 (45.0%), and 53 (24.1%) isolates, respectively [52]. Strains of salmonella enterica serotype typhimurium β-lactamase-producing resistant to ceftriaxone were isolated from stool specimens of patients and the minimum inhibitory concentration of ceftriaxone is 256 µg/ml and the resistance to ceftriaxone is caused by the transfer of a 3.2-kb plasmid [53]. Three-hundred-twenty-seven strains of non-typhoid Salmonella enterica were isolated from stool of patients and the resistance is attributed to the genes CTX-M-14 β-lactamase and CMY-2 β-lactamase [54]. Episodes of spontaneous bacterial peritonitis with positive blood and/or ascitic culture were observed in 246 patients. In these patients the resistance to ceftriaxone is due to gram-negative bacilli with extended-spectrum β-lactamase-producing, other resistant gram-negative bacilli, and enterococci and the resistance of these bacteria to ceftriaxone is due to the previous use of cephalosporins [55]. The proportion of isolates of Enterobacter cloacae

resistant to ceftriaxone increased from 64.3% to 77.6% during the period 1999 to 2002 and the extent of resistance is correlated with the use of ceftriaxone [56].

Transfer of ceftriaxone across the human placenta

Ceftriaxone was administered intravenously at a daily dose of 1 gram to 133 pregnant women at the third trimester of pregnancy. The concentration of ceftriaxone ranged between 3.02 to 18.92 µg/ml in the umbilical cord venous serum and between 3.07 to 78.20 µg/ml in the maternal serum thus ceftriaxone is poorly transferred across the human placenta [57]. Ceftriaxone was administered intravenously at a daily dose of 2 grams to 17 pregnant women at term of pregnancy and Kafetzis et al. [58] determined the area under the concentration-time curve and the elimination half-life of ceftriaxone in maternal serum, in umbilical cord venous serum, in amniotic fluid, and in the placenta.

Table 3. Area under the concentration-time curve and elimination half-life of ceftriaxone which have been obtained in maternal serum, umbilical cord venous serum, amniotic fluid, and in placenta. Values are the mean, by Kafetzis et al. [58].

Parameter	AUC_{0-24h} (µg*h/ml)	Elimination half-life (h)
Maternal serum	652	6.0
Umbilical cord venous serum	234	7.0
Amniotic fluid	256	6.8
Placenta	162	5.4

AUC = area under the concentration-time curve from 0 to 24 hours.

This table shows that the area under the concentration-time curve obtained in umbilical cord venous serum is about one third of that in maternal serum suggesting that ceftriaxone is poorly transferred across the human placenta. The area under the concentration-time curve of ceftriaxone in amniotic fluid is similar to that in umbilical cord venous serum and the area under the concentration-time curve of ceftriaxone in the placenta is about one half of that in the umbilical cord venous serum. These results indicate that ceftriaxone resides mainly in maternal serum. The elimination half-life of ceftriaxone is about 6 hours in maternal serum, in umbilical cord venous serum, in amniotic fluid, and in placenta indicating that ceftriaxone is slowly eliminated from these compartments.

Migration of ceftriaxone into the breast-milk

Kafetzis et al. [58] determined the area under the concentration-time curve and the elimination half-life of ceftriaxone in maternal serum and the area under the concentration-time curve, the absorption and elimination half-live of ceftriaxone in breast-milk. Ceftriaxone was administered at a daily dose of 1 gram to 20 lactating women, 10 women received ceftriaxone intravenously and 10 women received ceftriaxone intramuscularly.

Table 4. Area under the concentration-time curve and elimination half-life of ceftriaxone which have been determined in maternal serum and area under the concentration-time curve and the absorption and elimination half-live of ceftriaxone which have been determined in the breast-milk. Ceftriaxone was administered at a daily dose of 1 gram. Values are the mean±SD, by Kafetzis et al. [58].

	Maternal serum		Breast-milk		
	AUC_{0-24} (µg*h/ml)	Elimination Half-life (h)	AUC_{0-24} (µg*h/ml)	Absorption half-life (h)	Elimination half-life (h)
Administration route (N)					
Intravenous (N = 10)	392±23.0	5.3±0.2	11.8±4.5	1.7±0.9	12.8±3.7
Intramuscular (N = 10)	379±56.3	5.3±0.4	21.0±2.5	1.7±0.2	17.3±2.1

AUC_{0-24} = area under the concentration-time curve from 0 to 24 hours.

This table shows that the area under the concentration-time curve of ceftriaxone is about 30-times lower in the breast-milk than in maternal serum indicating that ceftriaxone poorly migrates into the breast-milk. The elimination half-life of ceftriaxone is about 2.5-times longer breast-milk than is maternal serum indicating that ceftriaxone is eliminated more slowly in breast-milk than in maternal serum. The area under the concentration-time curve of ceftriaxone is higher following intramuscular than intravenous dosing. The absorption half-life of ceftriaxone in breast-mil is 1.7 hours indicating that ceftriaxone rapidly migrates into the breast-milk.

Discussion

Ceftriaxone is a third-generation cephalosporin and is resistant to many narrow-spectrum β-lactamases and has good activity against most gram-positive and gram-negative aerobic bacteria. Ceftriaxone has an elimination half-life of about 8 hours allowing for once-daily dosing for most indications. Ceftriaxone is the drug of choice to treat serious infections caused by Escherichia coli, Klebsiella, Proteus, Haemophilus influenzae, Moraxella catarrhalis, Citrobacter, Enterobacter, Serratia, Neisseria gonorrhoea, Staphylococcus aureus, Streptococcus pneumonia, and Streptococcus pyogenes, and for severe forms of Lyme disease. Ceftriaxone is used for the empiric treatment of meningitis in non-immunocompromised adults and children (in combination with vancomycin and ampicillin pending the identification of the causative agent) owing to its excellent activity against Haemophilus influenzae, sensitive Streptococcus pneumoniae, Neisseria meningitides, and gram-negative enteric bacteria. Ceftriaxone is used to treat community-acquired pneumonia, ureteral, cervical, rectal, and pharyngeal infections, all forms of gonorrhoea, and severe forms of Lyme disease. About half of ceftriaxone is recovered from the urine and the remainder is eliminated by biliary secretion [1]. The efficacy and safely of ceftriaxone have been reviewed. Ceftriaxone administered intravenously at a dose of 2 grams twice-daily effectively and safely treats patients with community-acquired pneumonia [2, 3]. Ertapenem and ceftriaxone administered intravenously at a dose of 1 gram once-daily have similar efficacy and safely in treatment of hospitalized patients with community-acquired pneumonia [4]. Ceftriaxone administered intravenously at a daily dose of 2 or 4 grams effectively and safely treats patients with amyotrophic lateral sclerosis [5], ceftriaxone administered intravenously at a daily dose of 250

mg effectively and safely treats patients with uncomplicated gonorrhoea [6], ceftriaxone administered intravenously at a daily dose of 2 grams effectively and safely treats paediatric patients with urinary-tract, lower respiratory-tract, skin, soft-tissue, bone and joint infections, bacteraemia, and septicaemia caused by gram-negative bacteria [7], treats serious infections caused by gram-negative bacteria in paediatric patients [8], and ceftriaxone administered intravenously at a dose of 50 to 80 mg/kg once-daily effectively and safely treats paediatric patients with infection caused by Haemophilus influenzae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumonia, or by Escherichia coli [9]. These results indicate that ceftriaxone administered intravenously at the daily dose of 1 gram or 2 grams effectively and safely treat infections caused by different bacteria. The pharmacokinetics of ceftriaxone have been studied in 12 patients with nosocomial pneumonia, intraabdominal sepsis, or urinary sepsis and ceftriaxone was intravenously infused at a dose of 2 grams once-daily. Then patients had normal renal function and 2 patients had renal failure [10]. The mean elimination half-life and the total body clearance of ceftriaxone are 6.4 hours and 41.3 ml/min, respectively, in 10 patients with normal renal function, and 21.4 hours and 19.9 ml/min, respectively, in 2 patients with renal failure. Ceftriaxone is eliminated in part by renal route thus the elimination half-life is longer in patients with renal failure than in patients with normal renal function. Consequently, the total body clearance of ceftriaxone is lower in patients with renal failure than in patients with normal renal function. The prophylaxis with ceftriaxone has been reviewed. Ceftriaxone administered intravenously at a daily dose of 2 grams prevents postoperative infections more effectively than other antibiotics [11], intravenous ceftriaxone plus intravenous metronidazole prevents the infection in children with perforated appendicitis more effectively than anti-pseudomonal antibiotics [12], intravenous ceftriaxone administered at a daily dose of 1 gram is more effective than norfloxacin administered orally at a dose of 400 mg twice-daily for the prophylaxis of bacterial infections in patients undergoing surgery [13], one single intravenous dose of 1 gram of ceftriaxone is effective as ampicillin/cloxacillin administered intravenously at a dose of 1 gram 3 times-daily in preventing complications during post-Caesarean section [14], intravenous ceftriaxone prevents surgical infections, urinary-tract infections, and respiratory-tract infections more effectively than another cephalosporin such as cefamandole, cefazolin, cefotaxime, or cefuroxime [15], and intravenous ceftriaxone administered at a daily dose of 2 grams prevents the infection in patients undergoing colorectal surgery more effectively than penicillins [16], a single intravenous dose of 2 grams of ceftriaxone administered at the induction of anaesthesia prevents the infection in patients undergoing orthopaedic surgery [17], ceftriaxone administered intravenously at a single dose of 2 grams before surgery and administered at an intravenous dose of 2 grams for 2 days after surgery prevent the infection in patients undergoing liver transplantation [18], ceftriaxone administered at an intragluteal daily dose of 2 grams prevents the infection in patients undergoing orthopaedic and traumatic surgery [19], ceftriaxone administered intravenously at a daily dose of 2 grams prevents post-operative pyrexia and infections in patients undergoing chest surgery and shorts the hospital stay [20], and ceftriaxone administered intravenously at a daily dose of 2 grams is more efficacious that placebo for the prevention of infections in patients undergoing chest surgery [21]. These results indicate that ceftriaxone administered intravenously at a daily dose of 1 gam or 2 grams prevents different infections. The treatment of bacterial infections with ceftriaxone has been reviewed. Intravenous ceftriaxone effectively treats neurosyphilis as intravenous benzylpenicillin [22], ceftriaxone administered intravenously at a dose of 2 grams once-daily treats endocarditis, spondylodiscitis, and prosthetic joint infections caused by Cutibacterium acnes [23], ceftriaxone administered intravenously at a daily dose of 1 or 2 grams for 3 to 6 days treats patients with uncomplicated and severe forms of leptospirosis [24], ceftriaxone administered intravenously at a daily dose of 2 grams treats patients with acute tonsillopharyngitis [25], a single intravenous dose of 2 grams of ceftriaxone treats patients with meningococcal meningitis [26], ceftriaxone administered intravenously at a daily dose of 3 grams for 7 days treats patients with typhoid fever [27], ceftriaxone administered intravenously once-daily at a dose of 2 grams for 4 weeks treats patients with streptococcal endocarditis [28], ceftriaxone administered intravenously at a dose of 1 gram 4 times-daily every 2 days treats patients with primary and secondary syphilis [29], intramuscular ceftriaxone treats patients with urinary-tract infection as intravenous trimethoprim-sulfamethoxazole [30], ceftriaxone administered intravenously at a dose of 2 grams once-daily for 14 days treats acute disseminated Borrelia burgdorferi infection as doxycycline administered orally at a dose of 100 mg twice-daily for 21 days [31], ceftriazone administered intravenously at a dose of 1 gram twice-daily treats patients with respiratory-tract, urinary-tract, skin, soft-tissue, bone and joint infections, catheter-relayed septicaemia, and otitis media [32], ceftriaxone administered intravenously at a dose of 1 gram once-daily treats patients with bacteriologically proven cellulitis, suppurative diabetic foot ulcer, and soft-tissue infections [33], ceftriaxone administered intravenously at a dose of 1 gram twice-daily treats patients with respiratory-tract, urinary-tract, skin, soft-tissue, bone, and joint infections caused by Staphylococcus aureus, aerobic gram-positive cocci, or by Pseudomonas aeruginosa [34], and ceftriaxone administered intravenously at a dose of 1 gram twice-daily treats patients with skin, soft-tissue, urinary-tract, biliary-tract infections, pneumoniae, and sinusitis caused by Staphylococcus epidermis, Streptococcus pneumoniae, Streptococcus faecalis, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Bacteroides fragilis, or by anaerobic cocci [35]. These results indicate that ceftriaxone administered intravenously treat different infections. The trials with ceftriaxone have been reviewed. Ceftriaxone administered intravenously at a dose of 2 grams twice-daily for 3 days is more effective than placebo in treating gallbladder infection and diarrhoea caused by Clostridium difficile [36], ceftriaxone administered intravenously at a dose of 2 grams once-daily is effective as multiple dosing regimens of anti-staphylococcal antibiotics in treating patients infected by methicillin-susceptible staphylococcus aureus [37], ceftriaxone administered intravenously at a daily dose of 1 gram is effective as ceftriaxone administered intravenously at a daily dose of 2 grams in treating patients with community-acquired pneumonia [38], a 12-month follow-up resulted that ceftriaxone administered intravenously at a daily dose of 1 gram treats early syphilis as doxycycline, or tetracycline, or penicillin administered intravenously at a daily dose of 1 gram [39], ertapenem administered intravenously at a dose of 1 gram once-daily for 3 days is efficacy as ceftriaxone administered intravenously at a dose of 2 grams once-daily for 3 days in treating patients with acute pyelonephritis [40], ceftriaxone administered intravenously at a dose of 2 grams once-daily for 3 days is effective as cefditoren pivoxil administered orally at a dose of 400 mg once-daily for 3 days in treating patients with acute pyelonephritis [41], ceftriaxone administered intravenously at a daily dose of 2 grams is 3 times more effective than ampicillin/sulbactam administered intravenously at a daily dose of 3 grams in treatment of patients with postoperative neurosurgical infections [42], and ceftriaxone administered intravenously at a daily dose of 2 grams is effective as cefotaxime administered intravenously at a dose of 2 grams 4 times-daily in treating serious bacterial infections [43]. These results indicate that ceftriaxone administered intravenously is efficacy as other antibiotics in treatment of different bacterial infections. The penetration of ceftriaxone into the cerebrospinal has been reviewed. Ceftriaxone was administered intravenously at a dose of 2 grams twice-daily for 3 days to 7 patients with uninflamed meninges. The mean time to reach the peak concentration of ceftriaxone in the cerebrospinal fluid is 11.4 hours indicating that ceftriaxone penetrates slowly into the cerebrospinal fluid. The mean ratio of the area under the concentration-time curve of ceftriaxone in the cerebrospinal fluid to that in serum is 0.0076 indicating that ceftriazone resides mainly is serum. The mean peak concentration of ceftriaxone in the cerebrospinal fluid is 0.53 µg/ml, this concentration is higher the minimum inhibitory concentration of

Neisseria meningitidis Haemophilus influenzae, penicillin G-sensitive Streptococcus pneumonia, Borrelia burgdorferi and some Enterobacteriaceae by approximately 10-fold thus ceftriaxone is bactericidal. The mean elimination half-life of ceftriaxone in the cerebrospinal fluid is 17.0 hours indicating that ceftriaxone is slowly eliminated from the cerebrospinal fluid [44]. Ceftriaxone was administered intravenously at a median daily dose of 6.5 grams (range, 4 to 9) corresponding to a median daily dose of 97.5 mg/kg (range, 77 to 131) to 16 patients with the meningitis caused by Streptococcus pneumoniae. The median concentration of ceftriaxone in the cerebrospinal fluid is 13.3 µg/ml (range, 0.9 to 91.2) this concentration is higher the minimum inhibitory concentration (0.5 µg/ml) of Streptococcus pneumoniae and the meningitis is cured in all patients [45]. Ceftriaxone was intravenously infused at a daily dose of 50 or 75 mg/kg to 17 paediatric patients with meningitis caused by Haemophilus influenzae. The concentration of ceftriaxone in the cerebrospinal fluid is 480 to 5,600-times higher the minimum inhibitory concentration of Haemophilus influenzae thus ceftriaxone is a useful agent to treat the meningitis caused by Haemophilus influenzae in paediatric patients [46]. These results indicate that ceftriaxone penetrates into the cerebrospinal fluid in concentration higher than the minimum inhibitory concentration of the organisms causing the meningitis. The treatment of bacterial meningitis with ceftriaxone has been reviewed. Ceftriaxone was administered intravenously at a daily dose of 100 mg/kg on day 1 followed by a daily dose of 80 mg/kg to patients with the meningitis caused by Haemophilus influenzae type b, or by Streptococcus pneumoniae, or by Neisseria meningitides. The concentration of ceftriaxone in the cerebrospinal fluid is 10 to 100-fold higher the minimum inhibitory concentration of the agents causing the meningitis at 24 hours after the start of treatment and is 5 to 50-fold higher the minimum inhibitory concentration of the organisms causing the meningitis at the end of therapy. Thus, ceftriaxone is an effective antibiotic to treat the meningitis caused by these organisms [47]. A single dose of 50 mg/kg of ceftriaxone was administered intravenously to patients with the meningitis caused by Neisseria meningitides, Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, Viridians streptococci, or by unknown organisms. The mean trough concentration of ceftriaxone in the cerebrospinal fluid is 3.5 µg/ml and the mean trough bactericidal titre is 1:128 thus a single intravenous dose of 50 mg/kg of ceftriaxone treats the meningitis caused by different bacteria [48]. Ceftriaxone was administered intravenously at a dose of 100 mg/kg once-daily to 53 infants and children and was administered intravenously at a dose of 60 mg/kg 4 times-daily to 53 infants and children. The meningitis was caused by Haemophilus influenzae and the cerebrospinal fluid becomes sterilized 18 to 36 hours after the start of treatment, the clinical response is similar according to the two treatments, and the meningitis is cured in all subjects [49]. These results indicate that ceftriaxone administered intravenously treats the meningitis caused by different bacteria in adults and in infants and children. The resistance of bacteria to ceftriaxone has been reviewed. The dissemination of extended-spectrum-β-lactamase-producing Salmonella isolates results in an increased prevalence of resistance to ceftriaxone and this resistance is increasing and constitutes a serious problem [50]. Multiple prescriptions of ceftriaxone and ceftriaxone misuse induce resistance to ceftriaxone in isolates of non-typhoid Salmonella and the resistance to ceftriaxone is in increasing problem and limits treatment options for serious infections caused by this organism [51]. The resistance of Salmonella producing β-lactamases to ceftriaxone is found in 33.6% of isolates and the resistance genes are blaCTX-M, blaTEM, and blaOXA which have been detected in 94.1%, 45.0%, and 24.1% isolates, respectively [52]. Strains of Salmonella enterica serotype typhimurium β-lactamase-producing become resistant to ceftriaxone, the minimum inhibitory concentration is 256 µg/ml, and the resistance to ceftriaxone is caused by the transfer of a 3.2-kb plasmid [53], strains of non-typhoid Salmonella enterica become resistant to ceftriaxone and the resistance is due to genes CTX-M-14 β-lactamase and CMY-2 β-lactamase [54], the resistance of gram-negative bacilli extended-spectrum β-lactamase-producing, other resistant gram-negative bacilli, and enterococci to ceftriaxone is due to the previous use of cephalosporins [55], and the resistance of Enterobacter cloacae to ceftriaxone increases from 64.3% to 77.6% during the period 1999 to 2002 and the extent of resistance is correlated with the use of ceftriaxone [56]. These results indicate that different bacteria may become resistant to ceftriaxone and the resistance to ceftriaxone is due to different mechanisms. The transfer of ceftriaxone across the human placenta has been reviewed. Ceftriaxone was administered intravenously at a daily dose of 1 gram to 133 pregnant women at the third trimester of pregnancy and the concentration of ceftriaxone ranges between 3.07 and 78.20 µg/ml in the maternal serum and between 3.02 and 18.92 µg/ml in the umbilical cord venous serum [57]. Ceftriaxone was administered intravenously at a daily dose of 2 grams to 17 pregnant women at term of pregnancy and the mean area under the concentration-time curve of ceftriaxone is 652 and 234 µg*h/ml in the maternal serum and in the umbilical cord venous serum, respectively. The elimination half-life of ceftriaxone is 6.0 and 7.0 hours in the maternal serum and in the umbilical cord venous serum, respectively, indicating that ceftriaxone is slowly eliminated in the maternal serum and in the umbilical cord venous serum [58]. These results indicate that ceftriaxone is poorly transferred across the human placenta. The migration of ceftriaxone into the breast-milk has been reviewed. The pharmacokinetics of ceftriazone were studied in the maternal serum and in the breast-milk of 20 lactating women receiving ceftriaxone. Ten lactating women received ceftriaxone intravenously at a daily dose of 1 gram and 10 lactating women received this dose of ceftriaxone intramuscularly [58]. The area under the concentration-time curve of ceftriaxone is about 33-fold higher in the maternal serum that in the breast-milk, the mean absorption elimination half-life of ceftriaxone is 1.7 hours. The mean elimination half-life of ceftriaxone is 12.8 and 17.3 hours following the intravenous and intramuscular administration of ceftriaxone, respectively. These results indicate that ceftriaxone poorly migrates into the breastmilk, is rapidly absorbed in the breast-milk and is slowly eliminated from the breast-milk.

In conclusion, ceftriaxone is a third-generation cephalosporin, is resistant to many narrow-spectrum β-lactamases, and has good activity against most gram-positive and gram-negative aerobic bacteria. Ceftriaxone is the drug of choice to treat serious infections caused by Escherichia coli, Klebsiella, Proteus, Haemophilus influenzae, Moraxella catarrhalis, Citrobacter, Enterobacter, Serratia, Neisseria gonorrhoea, Staphylococcus aureus, Streptococcus pneumoniae, and Streptococcus pyogenes, and for severe forms of Lyme disease. Single doses of intramuscular ceftriaxone have long been used in the management of ureteral, cervical, rectal, or pharyngeal gonorrhoea; increasing resistance has necessitated the use of higher doses. Half of ceftriaxone is eliminated by renal route and the remainder is secreted into the bile. The mean elimination half-life of ceftriaxone is 6.4 hours in patients with normal renal function and 21.4 hours in patients with renal failure thus the elimination half-life of ceftriaxone is longer in patients with renal failure. The prophylaxis, treatment and trials with ceftriaxone have been reviewed. Ceftriaxone penetrates into the cerebrospinal fluid in significant amounts and treats the meningitis caused by different bacteria. Ceftriaxone may become resistant to bacteria, is poorly transferred across the human placenta, and poorly migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of ceftriaxone.

Conflict of interests

The authors declare 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.

Acknowledgments

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio, of the Medical Library of the University of Pisa, for retrieving the scientific literature.

References

1. MacDougal C. "Cell Envelope: β-Lactam, Glycopeptide, and Lipopeptide Antibacterials". In The Goodman & Gilman's. The Pharmacological Basis of the Therapeutics, Brunton LL, and Knollmann BC, editors. Mc Graw Hill, 14th Edition, USA, New York. 2023; pp. 1147-1165.
2. Nakanishi Y, Ito A, Tachibana H, Ishida T, Mitsui M. Comparative prospective cohort study of the efficacy and safely according to dose of Ceftriaxone in community-acquired pneumonia. Eur Resp J. 2020; 56(64): 1783-1785.
3. Chaudhary M, Shiekh G, Ayub S, Mohd G, Mirfor. Comparative efficacy and safely analysis of CSE-1034 (ceftriaxone): An open labeled phase III study in community acquired pneumonia. J Inf Pub Health. 2018; 11(5): 691-697.
4. Ortiz-Ruiz G, Caballero-Lopez J, Friedland IR, Woods GL, Carides A. A study evaluating the efficacy, safely, and tolerability of ertapenem versus ceftriaxone for the treatment of community-acquired pneumonia in adults. Clin Infect Dis. 2002; 34(8):1076-1083.
5. Cudkowicz ME, Titus S, Kearney M, Yu H, Sherman A, Schoenfeld D, et al. Efficacy and safely of ceftriaxone for amyotrophic lateral sclerosis: results of a multi-stage, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Neurol. 2014; 13(11): 1083-1091.
6. Bai Z-G, Bao X-J, Cheng W-D, Yang K-H, Li Y-P. Efficacy and safely of ceftriaxone for uncomplicated gonorrhoea: a meta-analysis of randomized controlled trials. Int J STD AIDS. 2012; 23(2): 126-132.
7. Richards DM, Heel RC, Brogden RN, Speight TM, Avery GS. Ceftriaxone. A review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs. 1984; 27(6): 469-527.
8. Aronoff SC, Murdell D, O'Brien CA, Klinger JD, Reed MD, Blumer JL. Efficacy and safely of ceftriaxone in serious pediatric infections. Antimicrob Agents Chemother. 1983; 24(5): 663-666.
9. Frenkel LD. Once-daily administration of ceftriaxone for the treatment of selected serious bacterial infections in children. Pediatrics. 1988; 82(3 Pt 2): 486-491.
10. Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong EL, Gin T. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother. 2001; 47(4): 421-429.
11. Esposito S, Noviello S, Vanasia A, Venturino P. Ceftriaxone versus Other Antibiotics for Surgical Prophylaxis: A Meta-Analysis. Clin Drug Investig. 2012; 24(1): 29-39.
12. Hamdy RF, Handy LK, Spyridakis E, Dona D, Bryan M, Collins JL, et al. Comparative Effectiveness of Ceftriaxone plus Metronidazole versus Anti-Pseudomonal Antibiotics for Perforated Appendicitis in Children. Surg Infect (Larchmt). 2019; 20(5): 399-405.
13. Fernández J, del Arbol LR, Gómez C, Durandez R, Serradilla R, Guarner C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and haemorrhage. Gastroenterology. 2006; 131(4): 1049-1056.
14. Ahmed E-TS, Mirghani OA, Gerais AS, Adam I. Ceftriaxone versus ampicillin/cloxacillin as antibiotic prophylaxis in elective caesarean section. East Mediterr Health J. 2004; 10(3): 277-288.
15. Dietrich ES, Bieser U, Frank U, Schwarzer G, Daschner FD. Ceftriaxone versus other cephalosporins for perioperative antibiotic prophylaxis: a meta-analysis of 43 randomized controlled trials. Chemotherapy. 2002; 48(1): 49-56.
16. Rau HG, Mittelkötter U, Zimmermann A, Lachmann A, Köhler L, Kullmann KH. Perioperative infection prophylaxis and risk factor impact in colon surgery. Chemotherapy. 2000; 46(5): 353-363.
17. Mazza A. Ceftriaxone as short-term antibiotic prophylaxis in orthopedic surgery: a cost-benefit analysis involving 808 patients. J Chemother. 2000; 12 (Suppl 3): 29-33.
18. Grazi GL, Mazziotti A, Fisichella S, Scalzi E, Cavallari A. Antimicrobial prophylaxis with ceftriaxone for prevention of early postoperative infections after 49 liver transplantations. J Chemother. 2000; 12 (Suppl 3): 10-16.
19. Paul KJ, Hennig FF, Bartsch MM. Perioperative Prophylaxis in Orthopedic and Traumatic Surgery with Ceftriaxone. Eur Surg Res 1989; 21(3): 33-35.
20. el-Mufti M, F Rakas S, Glessa A, Abdulhadi A, Ekgam S, Fraitis F, et al. Ceftriaxone versus clavulanate-potentiated amoxycillin for prophylaxis against postoperative sepsis in biliary surgery: a prospective randomized study in 200 patients. Curr Med Res Opin. 1989; 11(6): 354-359.
21. Kiff RS, Lomax J, Fowler L, Kingston RD, Hoare EM, Sykes PA. Ceftriaxone versus povidone iodine in preventing wound infections following biliary surgery. Ann R Coll Surg Engl. 1988; 70(5): 313-316.
22. Bettuzzi T, Jourdes A, Robineau O, Alcaraz I, Manda V, Molina J, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study. Lancet Inf Dis. 2021; 21(10): P1441-P1447.
23. Tiltnes TS, Kehrer M, Hughes H, Morris TE, Justesen US. Ceftriaxone treatment of spondylodiscitis and other serious infections with Cutibacterium acnes. J Antimicrob Chemother. 2020; 75(10): 3046-3048.
24. Faucher J-F, Chirouze C, Hoen B, Leroy J, Hustache-Mathieu L, Estavoyer J-M. Short-course treatment with ceftriaxone for leptospirosis: a retrospective study in a single center in Eastern France. J Infect Chemother. 2015; 21(3): 227-228.
25. Al Alawi S, Abdulkarim S, Elhennawy H, Al-Mansoor A, Al Ansari A. Outpatient parenteral antimicrobial therapy with ceftriaxone for acute tonsillopharyngitis: efficacy, patient satisfaction, cost effectiveness, and safely. Infect Drug Resist. 2015; 8(8): 279-285.
26. Nathan N, Borel T, Djibo A, Evans D, Djibo S, Corty JF, et al. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. Lancet. 2005; 366(9482): 308-313.
27. Wallace MR, A Yousif A, Mahroos GA, Mapes T, Threlfall EJ, Rowe B, et al. Ciprofloxacin versus

ceftriaxone in the treatment of multiresistant typhoid fever. Eur J Clin Microbiol Infect Dis. 1993; 12(12): 907-910.
28. Francioli P, Etienne J, Hoigné R, Thys JP, Gerber A. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone sodium for 4 weeks. Efficacy and outpatient treatment feasibility. JAMA. 1992; 267(2): 264-267.
29. Schöfer H, Vogt HJ, Milbradt R. Ceftriaxone for the Treatment of Primary and Secondary Syphilis. Chemotherapy 1989; 35(5): 140-145.
30. Rosenberg JM, Levy RC, Cicmanec JF, Hedges JR, Burke BM. Single-dose ceftriaxone treatment of urinary tract infections. Ann Emerg Med. 1985; 14(10): 970-972.
31. Dattwyler RJ, Luft BJ, Kunkel MJ, Finkel MF, Wormser GP, Rush TJ, et al. Ceftriaxone compared with doxycycline for the treatment of acute disseminated Lyme disease. N Engl J Med. 1997; 337(5): 289-294.
32. Gainer RB. Ceftriaxone in treatment of serious infections. Skin and soft-tissue infections. Hosp Pract (Off Ed). 1991; 26(Suppl 5): 24-30.
33. Bradsher RW, Snow RM. Ceftriaxone treatment of skin and soft-tissue infections in a once daily regimen. Am J Med. 1984; 77(4): 63-67.
34. Bittner MJ, Dworzack DL, Preheim LC, Tofte RW, Crossley KB. Ceftriaxone therapy of serious bacterial infections in adults. Antimicrob Agents Chemother. 1983; 23(2): 261-266.
35. Epstein JS, Hasselquist SM, Simon GL. Efficacy of ceftriaxone in serious bacterial infections. Antimicrob Agents Chemother. 1982; 21(3): 402-406.
36. Gagnon DJ, Ryzhov SV, May MA, Riker RR, Geller B, May TL, et al. Ceftriaxone to PRevent pneumOnia and inflammaTion aftEr Cardiac arresT (PROTECT): study protocol for a randomized, placebo-controlled trial. Trials. 2022; 23(1): 197. doi: 10.1186.
37. Kamfose MM, Muriithi FG, Knight T, Lasserson D, Hayward G. Intravenous Ceftriaxone Versus Multiple Dosing Regimens of Intravenous Anti-Staphylococcal Antibiotics for Methicillin-Susceptible Staphylococcus aureus (MSSA): A Systematic Review. Antibiotics (Basel). 2020; 9(2): 39. doi: 10.3390.
38. Telles JP, Cieslinski J, Gasparetto J, Tuon FF. Efficacy of Ceftriaxone 1 g daily Versus 2 g daily for The Treatment of Community-Acquired Pneumonia: A Systematic Review with Meta-Analysis. Expert Rev Anti Infect Ther. 2019; 17(7): 501-510.
39. Liu H-Y, Han Y, Chen X-S, Bai L, Guo S-P, Li L, et al. Comparison of efficacy of treatments for early syphilis: A systematic review and network meta-analysis of randomized controlled trials and observational studies. PLoS One. 2017; 12(6): e0180001.
40. Park DW, Peck KR, Chung MH, Lee JS, Park YS, Kim HY, et al. Comparison of ertapenem and ceftriaxone therapy for acute pyelonephritis and other complicated urinary tract infections in Korean adults: a randomized, double-blind, multicenter trial. J Korean Med Sci. 2012; 27(5): 476-483.
41. Monmaturapoj T, Montakantikul P, Mootsikapun P, Tragulpiankit P. A prospective, randomized, double dummy, placebo-controlled trial of oral cefditoren pivoxil 400mg once daily as switch therapy after intravenous ceftriaxone in the treatment of acute pyelonephritis. Int J Infect Dis. 2012; 16(12): e843-e849.
42. Zhu XL, Wong WK, Yeung WM, Mo P, Tsang CS, K H Pang KH, et al. A randomized, double-blind comparison of ampicillin/sulbactam and ceftriaxone in the prevention of surgical-site infections after neurosurgery. Clin Ther. 2001; 23(8): 1281-1291.
43. Mandell LA, Bergeron MG, Ronald AR, Vega C, Harding G, Saginur R, et al. Once-daily therapy with ceftriaxone compared with daily multiple-dose therapy with cefotaxime for serious bacterial infections: a randomized, double-blind study. J Infect Dis. 1989; 160(3): 433-441.
44. Nau R, H Prange W, Muth P, Mahr G, Menck S, Kolenda H, et al. Passage of cefotaxime and ceftriaxone into cerebrospinal fluid of patients with uninflamed meninges. Antimicrob Agents Chemother. 1993; 37(7): 1518-1524.
45. Turnier PL, Grégoire M, Garot D, Guimard T, Duval X, Bernard L, et al. CSF concentration of ceftriaxone following high-dose administration: pharmacological data from two French cohorts. J Antimicrob Chemother. 2019; 74(6): 1753-1755.
46. Chadwick EG, Yogev R, Shulman ST, Weinfeld RE, Patel IH. Single-dose ceftriaxone pharmacokinetics in pediatric patients with central nervous system infections. J Pediatr. 1983; 102(1): 134-137.
47. Dankner WM, Connor JD, Sawyer M, Straube R, Spector SA. Treatment of bacterial meningitis with once daily ceftriaxone therapy. J Antimicrob Chemother. 1988; 21(5): 637-645.
48. Cabellos C, Viladrich PF, Verdaguer R, Pallares R, Liñares J, Gudiol F. A single daily dose of ceftriaxone for bacterial meningitis in adults: experience with 84 patients and review of the literature. Clin Infect Dis. 1995; 20(5): 1164-1168.
49. Schaad UB, Suter S, Gianella-Borradori A, Pfenninger J, Auckenthaler R, Bernath O, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. N Engl J Med. 1990; 322(3): 141-147.
50. Shi Q, Ye Y, Lan P, Han X, Quan J, Zhou M, et al. Prevalence and Characteristics of Ceftriaxone-Resistant Salmonella in Children's Hospital in Hangzhou, China. Front Microbiol. 2021; 12: 764787. doi: 10.3389.
51. Luvsansharav U-O, Wakhungu W, Grass J, Oneko M, Nguyen V, Bigogo G, et al. Exploration of risk factors for ceftriaxone resistance in invasive non-typhoidal Salmonella infections in western Kenya. PLoS One. 2020; 15(3): e0229581. doi: 10.1371.
52. Kuang D, Zhang J, Xu X, Shi W, Yang X, Su X, et al. Increase in Ceftriaxone Resistance and Widespread Extended-Spectrum β-Lactamases Genes Among Salmonella enterica from Human and Nonhuman Sources. Foodborne Pathog Dis. 2018; 15(12): 770-775.
53. Dimitrov TS, Udo EE, Verghese T, Emara M, Al-Saleh A. Plasmid-mediated high-level ceftriaxone resistance in a Salmonella enterica serotype typhimurium isolate. Med Princ Pract. 2006; 15(2): 145-148.
54. Li W-C, Huang F-Y, Liu C-P, Weng L-C, Wang N-Y, Chiu N-C, et al. Ceftriaxone resistance of nontyphoidal Salmonella enterica isolates in Northern Taiwan attributable to production of CTX-M-14 and CMY-2 beta-lactamases. J Clin Microbiol. 2005; 43(7): 3237-3243.
55. Ariza X, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, et al. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. J Hepatol. 2012; 56(4): 825-832.
56. Muller A, Lopez-Lozano JM, Bertrand X, Talon D. Relationship between ceftriaxone use and resistance to

third-generation cephalosporins among clinical strains of Enterobacter cloacae. J Antimicrob Chemother. 2004; 54(1): 173-177.

57. Şipoş SI, Dumitraşcu V, Popescu R, Daliborca C, Vlad DC. Maternal - Fetal transfer of ceftriaxone used for preoperative prophylaxis prior to cesarean section. Analytical approaches in a romanian clinical trial. Arch Bulkan Med Union. 2013; 54(1): 180-187.

58. Kafetzis DA, Brater DC, Fanourgakis JE, Voyatzis J, Georgakopoulos P. Ceftriaxone distribution between maternal blood and fetal blood and tissues at parturition and between blood and milk postpartum. Antimicrob Agents Chemother. 1983; 23(6): 870-873.

DOI: 10.31579/2688-7517/145