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# Clinical Pharmacology of Ceftriaxone in Neonates and Infants: Effects and Pharmacokinetics

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***Abstract***

Ceftriaxone is a versatile and useful "third-generation" cephalosporin that needs to be administered once-daily. Ceftriaxone is a β-lactamase-resistant cephalosporin. It is active against important gram-positive and most gram-negative bacteria. The $MIC_{90}$s of ceftriaxone are 0.1 µg/ml for Escherichia coli, 0.1 µg/ml for Klebsiella species, 0.2 µg/ml for Proteus species, 0.3 µg/ml for Enterobacter species, 0.4 µg/ml for Serratia species, 0.06 µg/ml for Streptococcus agalactiae, and 2 µg/ml for Staphylococcus aureus (β-lactamase producers). Ceftriaxone, like other cephalosporins, kills bacteria by interfering with the synthesis of cell walls. Ceftriaxone has a good penetration into the cerebrospinal fluid and is useful in the treatment of meningitis sustained by susceptible bacteria. The dose of ceftriaxone is 50 mg/kg per day in neonates and 100 mg/kg per day in older infants. Ceftriaxone has a longer half-life than other cephalosporins; the plasma half-life of ceftriaxone is 15 hours at birth and 7 hours over 2-4 weeks.

The mean distribution volume of ceftriaxone ranges from 0.497 to 0.608 l/kg, and is not different in neonates and infants. In neonates, the total body clearance is 0.28 ml/min/kg after single administration and 0.41 to 0.54 ml/min/kg after multiple ceftriaxone administrations. After single intramuscular administration of ceftriaxone, the time to reach the peak plasma concentration is 1.8 hours. This antibiotic displaces bilirubin from albumin binding sites, thereby increasing the amount of free bilirubin in plasma. Ceftriaxone should not be administered to infants with hyperbilirubinemia. The aim of this study is to review the effects and pharmacokinetics of ceftriaxone in neonates.

***Key Words***: Adolescents, Aggression, Children, Life Satisfaction, Self-rated Health.

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## 1- INTRODUCTION

Ceftriaxone is a versatile and useful "third-generation" cephalosporin that only needs to be given once-daily. Ceftriaxone displaces bilirubin from albumin binding sites and increases the unconjugated free bilirubin in plasma. It should only be given with great caution to any infants with high unconjugated plasma bilirubin level (1). Ceftriaxone is a β-lactamase-resistant cephalosporin first patented in 1979 that is active against some important gram-positive and most gram-negative bacteria. Because of good penetration in the cerebrospinal fluid, even when the meninges are not inflamed, it is now often used as a simpler alternative to cefotaxime in the treatment of meningitis due to organisms other than Listeria monocytogenes and faecal streptococci (enterococci). It is also used to treat Salmonella typhi infection in countries where this organism is becoming resistant to chloramphenicol, and also to treat gonorrhea (Neisseria gonorrhea 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. Ceftriaxone 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 adults (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 only limited information regarding its safety during human pregnancy is available. Very little of ceftriaxone appears in breast milk: the infant of any mother treated during lactation would be exposed to less than 1% of the maternal dose on weight-adjusted basis, and little of this would be absorbed. 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 infant syndrome). Severe, potentially lethal hemolysis, is another very rare complication (1). Ceftriaxone, like other cephalosporins, kills bacteria by interfering with the synthesis of their cell walls. They are most commonly used in hospitalized patients for prophylaxis because of their broad spectrum of activity. The agents often are inappropriately employed for both prophylaxis and empirical treatment because physicians lack knowledge of their true spectrum of activity. The "third-generation" cephalosporins are even more effective against aerobic gram-negative microorganisms than their precursors. Because of their unique pharmacokinetic properties, they are most useful to treat aerobic gram-negative bacterial meningitis and biliary tract infections. They should not be used as monotherapy to treat mixed infections or as empirical therapy for serious bacterial infections when staphylococci, streptococci, or anaerobes might be the etiologic agents.

The overutilization of all cephalosporins has resulted in increased rates of enterococcal superinfections because these microorganisms are not eradicated by this entire class of antibiotic (2). Ceftriaxone combines high intrinsic activity with a broad spectrum of action and good stability to hydrolysis by β-lactamases. The minimum inhibitory concentrations for 90% of organisms (MIC90s) of ceftriaxone for most neonatal microorganisms is extremely low when compared with attainable serum concentrations, e.g. Escherichia coli ($MIC_{90}$ = 0.1 µg/ml), Klebsiella species ($MIC_{90}$ = 0.1 µg/ml), Proteus species ($MIC_{90}$ = 0.2 µg/ml), Enterobacter species ($MIC_{90}$ = 0.3 µg/ml), Serratia species ($MIC_{90}$ = 0.4 µg/ml), Streptococcus agalactiae ($MIC_{90}$ = 0.06 µg/ml) and

Staphylococcus aureus (β-lactamase producers) ($MIC_{90}$ = 2 µg/ml) (3). Ceftriaxone is a safe and well tolerated antibiotic for use in the neonate. The high prolonged plasma half-life of ceftriaxone and its apparently good penetration in the cerebrospinal fluid, even through uninflamed meninges, offer hope that it may be useful in the treatment of meningitis sustained by susceptible organisms (4). Ceftriaxone has a broad spectrum of activity and improved β-lactamase stability (5).

It is active against most neonatal pathogens including Escherichia coli, Klebsiella species, Enterobacter species, Serratia species, Streptococcus agalactiae, Streptococcus pyogenes, Staphylococcus aureus, and Haemophilus influenzae (6). Comparative experimental and clinical studies have demonstrated ceftriaxone, a broad-spectrum β-lactamase-resistant cephalosporin, to be active against both aerobic and anaerobic gram-positive and gram-negative pathogens (7-9).

## 2- MATERIALS AND METHODS

### 2-1. Literature Search

The bibliographic search was performed electronically using PubMed database as search engine; April 2017 was the cutoff point.

### 2-2. Search Terms

The following key words "ceftriaxone effects neonates", "ceftriaxone safety neonates", "ceftriaxone susceptibility neonates", "ceftriaxone resistance neonates", and "ceftriaxone pharmacokinetics neonates" were used. In addition, the books Neonatal Formulary (1) and NEOFAX by Young and Mangum (10) were consulted.

## 3- RESULTS

### 2-1. Use:

Ceftriaxone is used for the treatment of neonatal sepsis and meningitis caused by susceptible gram-negative microorganisms (e.g. Escherichia coli, Pseudomonas aeruginosa, Klebsiella, Haemophilus influenzae) and for the treatment of gonococcal infections (10). Ceftriaxone distributes widely in cerebrospinal fluid, bile, bronchial secretions, lung tissue, ascitic fluid, and middle ear. Ceftriaxone is eliminated unchanged by both biliary (40%) and renal mechanisms. Serum half-life in premature infants is 5 to 16 hours. Dosage adjustment is necessary only for infants with combined hepatic and renal failures (10).

### 2-2. Dose and administration

**Sepsis and disseminated gonococcal infection:**

give 50 mg/kg intramuscularly, or preferably, intravenously once-daily for 7 days. Use with great caution in young infants with unconjugated jaundice (10).

**Meningitis:**

give 100 mg/kg loading dose, then 80 mg/kg once-daily (10).

**Uncomplicated gonococcal ophthalmia:**

give 50 mg/kg (maximum 125 mg) single dose. Note: topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is administered (10).

**Intravenous administration:**

infusion by syringe pump over 30 min. Avoid administration of calcium-containing solutions within 48 hours of the last administration of ceftriaxone (10).

**Intramuscular administration:**

to reduce pain at the injection site, reconstitute with 1% lidocaine without epinephrine (10).

**Neonatal gonococcal eye infection:**

give a single 125 mg intramuscularly dose of ceftriaxone. It was shown to be a simple

and very effective treatment strategy in one African trial (use 40 mg/kg in any low birth weight infant). Consider giving oral azithromycin or erythromycin as well if there is a possibility of chlamydial co-infection (1).

**Gonococcal infections:**

give 25 mg/kg per dose intravenously over 30 min of infusion or intramuscularly (10).

**Gonococcal ophthalmic prophylaxis in newborns whose mothers have gonorrhea at the time of delivery:**

give 100 mg/kg intravenously over 30 min of infusion or intramuscularly ceftriaxone. Topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is administered (10).

**Adverse effects and precautions:**

ceftriaxone is not recommended for use in neonates with hyperbilirubinemia because ceftriaxone displaces bilirubin from albumin binding sites increasing unconjugated plasma concentration. Concurrent administration of ceftriaxone and calcium-containing solutions is contraindicated. There have been 7 reported cases of cardiorespiratory arrest in young infants, with 6 deaths, associated with concurred administration of ceftriaxone and calcium-containing intravenous solutions. In all cases, the ceftriaxone dose (150 to 200 mg/kg/day) significantly exceeds the U.S.

Food and Drug Administration (FDA) recommended. Crystalline material or white precipitate was noted in vascular beds on autopsy (primarily in the lungs) in 4 of the 5 infants for which results were available. Ceftriaxone increases bleeding time, diarrhea and skin rash. Transient increase in blood urea nitrogen, serum creatinine, aspartate aminotransferase and alanine aminotransferase was observed. Transient gallbladder precipitations are occasionally associated with colicky abdominal pain, nausea and vomiting (10).

**Monitoring:**

complete blood count for eosinophilia, thrombocytosis, leucopenia, serum electrolytes, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, and bilirubin serum concentrations should be assayed. Consider abdominal ultrasonography (10).

### 2-3. Effects of ceftriaxone in neonates and infants

A group of 104 neonates with clinical signs of infection sufficient to justify treatment with penicillin plus gentamicin received instead monotherapy with ceftriaxone (50 mg/kg once-daily) (6). Bacterial cultures from 20 infants before treatment yielded significant isolates (9 had bacteremia). Following treatment, infecting bacteria were eradicated in 15 of 20 infants. Ten of the 104 infants died; all were examined post-mortem. Only one death was attributed to bacterial infection. The remaining neonates responded well to treatment. No adverse alterations in biochemical or hematological values were associated with ceftriaxone therapy. The incidence of diarrhea, blood in the stools, necrotizing enterocolitis or anti-coagulation problems was the same in infants not receiving ceftriaxone. Pharmacokinetic values were determined on 40 infants.

Elimination half-life and trough serum concentration decreased and the clearance increased with increasing post-natal age. Post-natal age was the single most significant factor affecting pharmacokinetics. Ceftriaxone is a safe and effective alternative to conventional therapy for infected neonates. Prolonged therapy is associated with superficial colonization with inherited resistant bacteria. Twenty-nine neonates with Streptococcus pneumoniae infection were identified from a total of 4,428 episodes of Streptococcus pneumoniae infection (11). Ninety percent of infants were ≥ 38 weeks'

gestation. The mean post-natal age was 18.1±8.2 days. Two mothers had bacterial infections at delivery; one had Streptococcus pneumoniae isolated from both blood and cervix, and one had clinical amnionitis. The primary diagnoses in the neonates were bacteremia (n = 8), meningitis (n = 8**),** Bacteremic pneumonia (n = 4), septic arthritis/osteomyelitis (n = 1), and otitis media (n = 8). Thirty percent of infants with invasive Streptococcus pneumoniae infection presented with leucopenia/neutropenia, but this did not predict poor outcome. The infecting pneumococcal serogroups were 19 (32%); 9 (18%); 3 and 18 (11% each); 1, 6 and 14 (7% each); and 5 and 12 (3.5% each).

Twenty-six percent of invasive neonatal infections were caused by serogroups 1, 3, 5, and 12, which were not contained in the heptavalent pneumococcal vaccine. In contrast, 6% of invasive non-neonatal disease was caused by these same non-vaccine serogroups. Susceptibility testing demonstrated that 21.4% of isolates were penicillin no-susceptible and 3.6% were ceftriaxone no-susceptible. Three (14.3%) neonates with invasive Streptococcus pneumoniae infection died; all deaths occurred within 36 hours of presentation.

Deaths did not appear to be related to pneumococcal serogroup or susceptibility. Compared with previous studies of neonates with pneumococcal infection, this series showed that infants with Streptococcus pneumoniae infection were 2 to 3 weeks of age at presentation, likely to be full term; and ill with pneumoniae, meningitis, and otitis media. This late-onset presentation was associated with an overall12 mortality of 10.3% (14.3% for invasive disease). Bradley et al. (12) described and summarized the reported cases that lead to safety concerns regarding the concurrent administration of intravenous ceftriaxone and calcium therapy in neonates and young infants. Nine reported cases were assessed. The Food and Drug Administration Adverse Event Reporting System database was searched for potential drug interactions in patients who were receiving concomitant ceftriaxone and calcium therapy. Eight of the reported 9 cases (7 were ≤ 2 months of age) represented possible or probable adverse drug events. There were 7 deaths. None of the cases were reported from the United States. 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 rate of occurrence of these serious adverse drug reactions cannot be accurately determined from available data. The concurrent use of intravenous ceftriaxone and calcium-containing solutions in the newborn and young infant may result in a life-threatening adverse drug reaction. Contributing factors for infants may include the use of ceftriaxone at dosages higher than those approved by the Food and Drug Administration, intravenous "push" administration, and administration of the total daily dosage as a single infusion.

Laga et al. (13) conducted a randomized clinical trial comparing a single intramuscular dose of 125 mg ceftriaxone with a single intramuscular dose of 75 mg of kanamycin followed by topical gentamicin for 7 days, and with a single intramuscular dose of 75 mg of kanamycin followed by topical tetracycline for 7 days, in the treatment of gonococcal ophthalmia neonatorum. Of 122 newborns with culture-proved gonococcal ophthalmia neonatorum, 105 infants returned for follow-up. Sixty-six (54%) of the Neisseria gonorrhea isolates were penicillinase producing. All 55 newborns who received ceftriaxone and returned for follow-up were clinically and microbiologically cured. One of 26 returning newborns who received kanamycin plus tetracycline and 2 of 24 returning newborns who received kanamycin plus gentamicin had persistent

or recurrent gonococcal conjunctivitis. Ceftriaxone also eradicated oropharyngeal gonococcal infection in 18 newborns, whereas oropharyngeal infection persisted in 2 of 8 newborns who had received kanamycin. Laga et al. (13) concluded that 125 mg of ceftriaxone as a single intramuscular dose is a very effective therapy for gonococcal ophthalmia neonatorum, with marked efficacy against extraocular infection and without the need for concomitant topical antimicrobial therapy. Because of high rates of neonatal gram-negative sepsis in many Latin American countries, Saez-Llorens et al. (14) prospectively enrolled 784 high-risk pregnant women in a study designed to evaluate the effect of a single 1 gram dose of ceftriaxone (n = 390) versus that of no antibiotic prophylaxis (n = 394) on oral, rectal, and umbilical colonization and fatality rates among newborn infants. The mean ceftriaxone concentration in cord blood samples was 26 µg/ml (range, 9 to 40 µg/ml).

Compared with infants of untreated mothers, infants born to women who were given ceftriaxone were colonized at a lesser rate by gram-negative bacilli (54% versus 3.1%, p-value = 0.001) and by group B streptococci (54% versus 21%, p-value = 0.03) and endured significantly fewer sepsis-like illnesses in the first 5 days of life (8.1% versus 3.1%, p-value = 0.06). Sepsis-related case-fatality rates (0.8% and 0.3%, respectively) were not significantly different. Although intrapartum administration of a single dose of ceftriaxone to high-risk mothers could be a safe and potentially useful strategy for reducing early-onset neonatal infections, additional information is required before this approach can be recommended for routine prophylaxis. Citrobacter meningitis is an uncommon enteric gram-negative infection that afflicts neonates and young infants. Approximately 30% of children treated or untreated die from the infection. Rae et al. (15) reported a cause of Citrobacter freundii meningitis that was resistant to ampicillin and was successfully treated with ceftriaxone. A 13-day-old, full-term neonate was admitted to the hospital with a one-day history of fever up to 38.8 degrees centigrade. On admission the infant had a temperature of 39.2 degrees centigrade, pulse of 140 beats/min, and a respiratory rate of 32 breaths/min. Except for a slightly bulging fontanelle, the rest of the physical examination was within normal limits. Complete blood count revealed a white blood cell count of 12.5 x $10^9$/l, with 0.66 polymorphonuclear cells, 0.10 bands, 0.18 lymphocytes, and 0.06 monocytes. A stat lumbar puncture showed 10 white blood cells per high-power field with gram-negative rods. Empiric therapy with ampicillin 225 mg every 12 hours and gentamicin 11 mg every 8 hours was started. Both antibiotics were discontinued after culture and sensitivity results were positive for Citrobacter freundii in the blood and spinal fluid. The neonate was successfully treated for nine days of ceftriaxone 250 mg every 12 hours.

### 2-4. Ceftriaxone displaces bilirubin from albumin binding sites

The in vivo bilirubin-albumin binding interaction of ceftriaxone was investigated in 14 non-jaundiced newborns, aged 33 to 42 weeks of gestation, during the first few days of life after they had reached stable clinical condition (16). 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 albumin concentration at baseline, at the end of ceftriaxone infusion, and at 15 and 60 min thereafter. Immediately after the end of drug administration, the reserve albumin concentration decreased from 91.9$\pm$25.1 µmol/l to 38.6$\pm$10.1 µmol/l (p-value = 0.0001). At the same

time the plasma bilirubin toxicity index increased from 0.64±0.40 before drug 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 drug infusion. Average total serum bilirubin concentrations decreased from a baseline value of 59.6±27.0 µmol/l to 55.2±27.1 µmol/l (p-level = 0.026). Sixty min after the end of ceftriaxone infusion, the reserve albumin concentration was 58.3±21.7 µmol/l, plasma bilirubin toxicity index regained baseline, but the displacement factor was still 1.9±0.2. No adverse events were recorded. These results demonstrate significant competitive interaction of ceftriaxone with bilirubin-albumin binding in vivo. Thus, ceftriaxone should not be given to neonates at risk of developing bilirubin encephalopathy.

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 (17). This study, performed on blood samples from icteric neonates, showed that the addition of ceftriaxone produced an increase of free bilirubin in plasma 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.

### 2-5. Safety profile of ceftriaxone in neonates and infants

Monte et al. (18) provided a comprehensive review of the literature surrounding the safety of ceftriaxone in the neonatal (< 28 days of post-natal age) and geriatric populations (age > 65 years). Ceftriaxone should be avoided or significantly minimized in neonates (especially those treated concomitantly with intravenous calcium solutions and those with hyperbilirubinemia), and potentially restricted in the geriatric population treated concomitantly with intravenous calcium. The safety of ceftriaxone was evaluated in 80 neonates who were treated empirically for suspected infection with either ceftriaxone and ampicillin (group A, post-natal age 0 to 72 hours) or ceftriaxone and vancomycin (group B, post-natal age greater than 72 hours) (19). Within 48 hours after birth 2 infants in group A died from sepsis due to Haemophilus influenzae and Streptococcus pneumoniae 1 case each); 1 infant in group B died for infection due to Pseudomonas aeruginosa. All bacterial isolates from group A infants, were susceptible to ceftriaxone but in 4 of the 8 group B infants with positive cultures a change in antibiotic therapy was required. Eosinophilia, thrombocytosis and increase in serum alkaline phosphatases were observed in a limited number of infants during and after discontinuation of treatment. Direct hyperbilirubinemia (> 2 mg/dl) occurred in 2 cases during treatment. Gallbladder sludge was sonographic diagnosed in 6 infants, but disappeared within 2 weeks after detection. One neonate had exanthema. Nurses rated ease of administration as very good. Ceftriaxone appears to be an interesting alternative in the empiric antibiotic treatment in the early neonatal period.

The pharmacokinetics and safety of ceftriaxone were examined in 39 neonates who required antibiotics for clinically suspected sepsis (4). The drug was administered as once-daily at the dose of 50 mg/kg by the intravenous or intramuscular route. Ceftriaxone was assayed in 49 series of blood samples, and 3 samples of cerebrospinal fluid by a microbiological technique. Blood was collected before, during and after treatment for biochemical analysis. Routine hematological investigations were also monitored. There was no significant difference between the peak plasma

concentrations following intravenous (153±39 µg/ml) or intramuscular (141±19 µg/ml) administration (first dose). The mean elimination half-life, total body clearance, and distribution volume were 15.4±5.4 hours, 0.28±0.12 ml/min/kg and 325±59 ml/kg, respectively. Clearance increased with increasing post-natal 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). There were no drug-associated changes in any of the biochemical or hematological parameters examined. Ceftriaxone is a safe and well tolerated antibiotic for use in the treatment of newborn sepsis and possibly meningitis. A once-daily administration of 50 mg/kg by intravenous or intramuscular route provides satisfactory plasma concentrations throughout the dosage interval whilst avoiding accumulation.

Steele and Bradsher (20) evaluated the efficacy and safety of ceftriaxone in 30 pediatric and 12 young adult patients with serious bacterial infections. Ceftriaxone was administered intravenously to children at a dosage of 50 to 75 mg/kg/day in two divided doses. Those with central nervous system infections received 100 mg/kg/day. In adults, the dosage was 1 gram either once or twice daily. The diseases treated included pneumonia (n = 17), sepsis (n = 8), ventriculoperitoneal (VP) shunt infections (n = 3), osteomyelitis (n = 3), brain abscesses (n = 2), peritonitis (n = 2), and miscellaneous (n = 7). Clinical cures were achieved in all cases, although one child with cystic fibrosis and Pseudomonas pneumonia infection had persistent colonization in his sputum. No serious side effects were observed. Although not the agent of choice for many of these pathogens, ceftriaxone appears to represent an important alternative to therapy.

### 2-6. Bacterial susceptibility to ceftriaxone and other antibiotics

Neonatal meningitis is caused by group B streptococci, Escherichia coli, and Listeria monocytogenes, in order of frequency. Newly developed cephalosporins with a broad spectrum of activity have altered the therapy of meningitis due to gram-negative bacilli. However, Bradsher and Ulmen (21) found that clinical isolates of group B streptococci and Listeria monocytogenes did not demonstrate uniform susceptibility to β-lactam antibiotics. Antibiotic potencies for group B streptococci tested were: cefotaxime, penicillin, ceftriaxone, amoxicillin, cefamandole, cephalotin, and moxalactam. N-formimidoyl thienamycin was most active against Listeria monocytogenes followed by penicillin, cephalotin and chloramphenicol; broad-spectrum cephalosporins were not active against Listeria organisms that were tested. These agents should not be utilized as solitary therapy of meningitis until the microorganisms have been characterized with antibiotic susceptibilities.

Neonatal meningitis is an important cause of morbidity. Swann et al. (22) described the etiology, antimicrobial susceptibility and suitability of the World Health Organization (WHO) first-line recommended antibiotics (penicillin and gentamicin) for bacterial meningitis in young infants in Malawi. Swann et al. (22) identified 259 culture-positive isolates from 259 infants ≤ 2 months of age. Sixty isolates were from neonates ≤ 7 days old, in whom the most common pathogens were group B Streptococcus (27/60; 45.0%), Streptococcus pneumoniae (13/60; 21.7%) and nontyphoidal Salmonella enterica (7/60; 11.7%). One hundred and ninety one isolates were from young infants who were < 7 days and ≤ 2 months of age. In this group, the most common isolates were Streptococcus pneumoniae (80/191; 41.9%), group B Streptococcus (38/191; 19.9%) and nontyphoidal

Salmonella enterica (34/191; 17.8%). More isolates were more susceptible to ceftriaxone than to the combination of penicillin and gentamicin (218/220; 99.1% versus 202/220; 91.8%, Fisher's exact test p-value = 0.006). Penicillin and gentamicin provided less coverage for gram-negative than gram-positive isolates (74/86; 86.0% versus 155/163; 95.1%, r = 6.24, p-value = 0.012). In view of these results, the World Health Organization recommendations for empiric penicillin and gentamicin for suspected neonatal meningitis should be reevaluated.

Streptococcus agalactiae is known to be the major cause of neonatal infections and also causes complications during pregnancy (23). One hundred and six strains of Streptococcus agalactiae recovered from clinical specimens of newborns (n = 18) and pregnant women (n = 88) were submitted to antimicrobial susceptibility testing and investigation of genetic determinants of macrolide resistance, capsular type, and virulence factors. Genetic diversity was evaluated by pulsed-field gel electrophoresis. Strains were susceptible to ceftriaxone, levofloxacin, penicillin G, and vancomycin and resistant to tetracycline (85.8%) and erythromycin (4.7%).

A total of 190 respiratory pneumococcal isolates obtained from children aged from 0 to 14 years were isolated and identified by using standard microbiological methods. Susceptibility to oxacillin, erythromicin, clindamycin, tetracycline, cotrimoxazole, ofloxacin, and rifampicin was tested by disc diffusion method (24). MIC for amoxicillin and ceftriaxone were determined by means of E-test. All tested isolates were susceptible to amoxicillin and ceftriaxone. The minimal amoxicillin concentration inhibiting the growth of 50% of isolates and 90% of isolates was 0.50 µg/ml and 1.0 µg/ml, respectively, and the minimal ceftriaxone concentration inhibiting the growth of 50% isolates and 90% isolates was 0.25 µg/ml and 0.50 µg/ml, respectively. Surveys of the nasopharyngeal carriage Haemophilus influenzae in children younger than 5 years of age with acute respiratory tract infection were conducted in Beijing children's hospital in China in 2000, 2002, 2010, and 2012 (25). The overall annual carriage rates of Haemophilus influenzae among children younger than 5 years of age with acute respiratory tract infection were 35.5%, 20.6%, 14.4%, and 18.7%, respectively, and the percentages of Haemophilus influenzae isolates producing β-lactamase were 4%, 13%, 27.1% and 31%, respectively. The percentages of susceptibility to ampicillin progressively decreased from 96% (2000) to 87% (2002) to 63% (2010) and to 61% (2012). All of the ampicillin-resistant isolates were found to be β-lactamase producers. The susceptibility to tetracycline increased from 54% (2000), to 60% (2002), to 91.5% (2010), and to 94.5% (2012). No statistically significant differences were observed in cefaclor, cefuroxime, sulfamethoxazole, and chloramphenicol. Amoxicillin/clavulanic acid and ceftriaxone were the most effective antimicrobials for the isolates of Haemophilus influenzae across the 10-year period.

### 2-7. Bacteria resistance to ceftriaxone and other antibiotics

A total of 16 isolates of Salmonella enterica were recovered from 16 infants hospitalized. All these neonates developed diarrhea, and 3 of them developed septicemia (26). All isolates demonstrated resistance to ceftriaxone and ceftazidime due to the production of a extended-spectrum β-lactamase. The isolates were also resistant to aminoglycosides (kanamycin, tobramycin, netilmicin, gentamicin, and amikacin) and sulfamethoxazole-trimethoprim. DNA profiles were determined by pulsed-field

gel electrophoresis using the Xbal and Spel endonucleases and by ribotyping with Psti digestion. They yielded the same patterns, showing that the outbreak was caused by a single clone. The extended-spectrum β-lactamase resistance was identified as CTX-M-27 by sequencing of Polymerase chain reaction (PCR) products and isoelectric focusing. The extended-spectrum β-lactamase resistance was transferred by a 40-kb conjugative plasmid. The mobile insertion sequence insertion sequence (IS) ISEcp1 was found to be located upstream of bla(CTX-M-27) in the same position as known for a bla(CTX-M-14) sequence. A new gene named dfrA21, encoding resistance to trimethoprim and carried by a 90-kb plasmid, was characterized. The dfrA21 gene was inserted as a single resistance cassette in a class I integron. The infants were treated with colistin, and all accepted two recovered. The outbreak came to an end when appropriate actions were taken: patient isolation, and washing, and disinfection of the ward.

A total of 34 stool specimens were obtained from preterm infants upon admission and once weekly up to two weeks during hospitalization (27). The presumptive colonies of Escherichia coli and Klebsiella pneumoniae were selected for identification, antibiotic susceptibility testing, and subtyping by using pulsed-field gel electrophoresis. Out of 76 gram-negative isolates, highest resistance was detected for amoxicillin/clavulanate (30.8%, n = 16), ceftriaxone (42.3%, n = 22), ceftazidime (28.8%, n = 15), cefoxitin (28.8%, n = 15), aztreonam (36.5%, n = 19), and polymyxin B (23.1%, n = 12). Three colistin resistant Klebsiella pneumoniae have also been detected based on E-test analysis. Thirty-nine isolates of Klebsiella pneumoniae and 20 isolates of Escherichia coli were resistant to more than three antimicrobial classes and were categorized as multidrug resistant. Pulsed-field gel electrophoresis analysis revealed higher diversity in pulsotypes for Klebsiella pneumoniae (18 pulsotypes) in comparison to Escherichia coli (4 pulsotypes). In addition, a total of fifteen pulsotypes was observed from 39 multidrug resistant Klebsiella pneumoniae. The risk factors for antibiotic resistance were assessed using random forest analysis. Gender was found to be the most important predictor for colistin resistant while length, Optical Fiber Communication (OFC), and delivery mode showed showing greater predictive power in the polymyxin B resistance. These data revealed worrying prevalence rates of intestinal carriage of multidrug-resistant Klebsiella pneumoniae and Escherichia coli of hospitalized preterm infants in Malaysia, with particularly high resistance to polymyxins.

Three hundred and thirty neonates were recruited. Culture proven sepsis was noted in 24% (74/330) of the study participants (28). Isolated bacterial pathogens were predominantly Staphylococcus aureus, Klebsiella species and Escherichia coli. Klebsiella species 32.7% (17/52) was the predominant blood culture isolate in neonates aged below seven days while Staphylococcus aureus 54.5% (12/22) was commonest among those aged above seven days. Staphylococcus aureus was the predominant plus swabs isolates for both neonates aged 0 to 6 days 42.2% (98/232) and 7 to 28 days 52.3% (34/65). Resistance of blood culture isolates was high to ampicillin 81.1% (60/74) and cloxacillin 78.4% (58/74), moderate to ceftriaxone 14.9% (11/74) and cefuroxime 18.9% (14/74), and low to amikacin 1.3% (1/74). Isolates from swabs had high resistance to ampicillin 89.9% (267/297) and cloxacillin 85.2% (253/297), moderate resistance to ceftriaxone 38.0% (113/297) and cefuroxime 36.0% (107/297), and low resistance to amikacin 4.7% (14/297). Sepsis was higher in neonates with fever

and hypothermia (p-value = 0.02), skin pustules (p-value < 0.001), umbilical pus discharge and abdominal wall hyperemia (p-value = 0.04). Presence of skin pustules was an independent predictor of sepsis odds ratio (OR) 0.26, 95% confidence interval (0.1 to 0.66) (p-value = 0.004). The overall death rate was 13.9% (46/330), being higher in neonates with sepsis 24.3% (18/74) than those without infection 10.9% (28/256), p-value = 0.003. Staphylococcus aureus was the predominant isolate followed by Klebsiella and Escherichia coli. There was high resistance to ampicillin and cloxacillin. Mortality rate due to neonatal sepsis was high. Routine antimicrobial surveillance should guide the choice of antibiotics for empirical treatment of neonatal sepsis.

A total of 130 neonates with sepsis who were found to be blood culture positive were taken in the study by Najeeb et al. (29). Out of 130 culture proven cases of neonatal sepsis, gram-negative bacteria were found in 71 (54.6%) cases and gram-positive bacteria in 59 (54.6%) cases. Staphylococcus aureus was the most common bacteria found in 35 (26.9%) cases followed by Escherichia coli in 30 (23.1%) cases. Acinetobacter species, Staphylococcus epidermis, Klebsiella, streptococci, Enterobacter cloacae, and Moraxella species were found in 17 (13.1%), 17 (13.1%), 13 (10.0%), 7 (5.4%), 6 (4.6%), and 5 (3.8%) cases, respectively. In most cases causative organisms were found to be resistant to commonly used antibiotics like ampicillin, amoxicillin, cefotaxime, and ceftriaxone (77.7%, 81.5%, 63.1%, and 66.9%, respectively).

Silverstein et al. (30) determined whether reduced penicillin or ceftriaxone susceptibility affects clinical presentation and outcome in children with pneumococcal bacteremia. A total of 922 cases of pneumococcal bacteremia were reviewed. Of 744 isolates with penicillin susceptibilities, 56 were penicillin-nonsusceptible. The majority displayed intermediate resistance; 14 of 730 isolates with known ceftriaxone susceptibilities were ceftriaxone-nonsusceptible. Neither the penicillin- nor the ceftriaxone-nonsusceptible cohort displayed a difference from its susceptible counterpart in temperature, respiratory rate or white blood cell count on initial patient evaluation, although trend suggested they were more often admitted at the initial visit. At follow-up only children treated initially with antibiotic were evaluated. Children with penicillin-nonsusceptible isolates were no more likely to be febrile than those with penicillin-susceptible isolates (28% versus 25%, p-value = 0.61) or a new focal infection (10% versus 6%, p-value = 0.79).

Data concerning ceftriaxone-nonsusceptible organisms were limited by the low number of such isolates. Although patients with ceftriaxone-nonsusceptible pneumococci were more likely to be febrile at follow-up than those with ceftriaxone-susceptible organisms (67% versus 24%, p-value = 0.04), Silverstein et al. (30) were unable to demonstrate a significant difference for other endpoints. Reduced antibiotic susceptibility does not alter the clinical presentation of pneumococcal bacteremia. With current practice intermediate resistance to penicillin is of little clinical significance in non-meningitis system pneumococcal infection.

### 2-8. Pharmacokinetics of ceftriaxone in neonates and infants

Steele et al. (31) studied the pharmacokinetics of ceftriaxone in 5 full-term neonates, 8 to 21 days old, and 25 infants aged between 6 weeks to 2 years. The study was randomized so that half of the patients received 50 mg/kg ceftriaxone and half of patients received 75 mg/kg of ceftriaxone by intravenous infusion.

Plasma samples were obtained just before infusion and 15, 30, and 60 min and 2, 4, 6, and 10 hours after infusion. The kinetic parameters of ceftriaxone are summarized in **Table.1** (*Please see the table in the end of paper*). Results for five neonates, all over 7 days of life, were not different from those of older infants, so determinations were combined for analysis. A sample of cerebrospinal fluid was obtained for analysis of ceftriaxone concentration and it was 5.4 µg/ml and 6.4 µg/ml after the administration of 50 mg/kg and 75 mg/kg ceftriaxone, respectively. Compared with other β-lactam antibiotics, ceftriaxone exhibited the longest half-life and duration of bactericidal activity and was the most effective in reducing bacterial counts of Escherichia coli and group B streptococcus type III test strains in cerebrospinal fluid. Initial pharmacokinetic data in normal adult volunteers indicated an elimination half-life of approximately 8 hours (32, 33).

Similar studies in 5 infants and 5 young children demonstrated a slightly lower half-life of 6.5 hours (34). Most important for the treatment of meningitis are data concerning the penetration of antibiotics into cerebrospinal fluid. Cerebrospinal fluid levels 5 to 10% of concomitant plasma concentrations are comparable to those previously reported in animal models (35) and human studies (36). These cerebrospinal fluid levels exceeded the MICs for common pathogens by at least 10-fold; this appears to be the most critical determining factor for success therapy. Steele et al. (31) found that ceftriaxone penetrated into the cerebrospinal fluid of infants and neonates to a degree that should provide adequate levels to treat the usual bacterial causes of meningitis. The measured plasma half-life was longer than those of other cephalosporins and investigational β-lactam antibiotics, ensuring a greater duration of bactericidal activity for individual doses. These initial pharmacokinetic data establish a tentative dosage schedule of 50 mg/kg every 12 hours for the treatment of meningitis in infants over 7 days of age. Mulhall et al. (4) investigated the pharmacokinetics of ceftriaxone in 39 neonates of mean birth weight 1,800±860 grams (range, 710 to 4,000 grams). The gestational age was 31.7±4.0 weeks (range, 26 to 41 weeks). Ceftriaxone was administered as a single daily intravenous infusion of 50 mg/kg. The drug was administered as an intravenous or intramuscular injections. Although plasma concentrations were higher in the first 2-3 hours of the dosage interval following multiple intramuscular injections, the serum concentration/time curve declined more rapidly than following the first injection because the half-life of ceftriaxone decreased ($r = 0.3754$; p-value $< 0.001$) and clearance increased ($r = 0.5031$; p-value $< 0.0002$) with increasing post-natal age.

Consequently, no accumulation of ceftriaxone occurred. There was no significant difference in peak concentration of ceftriaxone following intravenous or intramuscular administration. The clearance increased also with increasing body temperature ($r = 0.4497$; p-value $< 0.002$) and decreasing plasma creatinine concentration ($r = -0.4003$; p-value $< 0.01$). Older neonates exhibited lower trough plasma concentrations ($r = -0.4402$; p-value $< 0.003$) and shorter half-lives ($r = -0.3754$; p-value $< 0.01$). Increasing plasma protein concentration was associated with a decrease in the distribution volume ($r = -0.4504$; p-value $< 0.001$) and an increase in peak ceftriaxone ($r = 0.4515$; p-value $< 0.002$). The concentration of ceftriaxone in the lumbar cerebrospinal fluid of 3 neonates, with not-inflamed meninges, ranged between 2.1 and 3.8 µg/ml. **Table.2** shows the concentrations of ceftriaxone at various sampling times after intramuscular and intravenous administrations (*Please see the table in the*

*end of paper*). **Table.3** summarized the plasma pharmacokinetic parameters of ceftriaxone in 39 neonates (*Please see the table in the end of paper*). Intramuscular ceftriaxone results in peak plasma concentrations equivalent to those following intravenous administration. Although time-to-maximum (Tmax) was 1.5 hours, levels > 100 ng/mL were recorded within 15 min of intramuscular injection after multiple doses. Therefore, the only drawback to intramuscular administration are the painful injections which necessitate the use of lignocaine. The plasma elimination half-life was considerably longer and the clearance was lower than has been reported in infants (37). As renal and hepatic functions improve after birth, elimination of ceftriaxone becomes more rapid in infants than in neonates. Sixty percent of ceftriaxone is eliminated via the kidneys and decreased clearance in neonates is associated with raised plasma creatinine concentration. The slow rate of ceftriaxone elimination is thought to be due to the presence of an enolate an ion group in the 3-substituent of the molecule (38), its high degree of protein binding (90% in adults) and lack of tubular secretion. There were no drug-associated changes in any of the biochemical parameters examined other the fluctuations normally observed in this age group. There were no adverse effects on hematological parameter. No increase in the incidence of bloody stools over that normally observed in this population was associated with the use of ceftriaxone.

Sato (39) reported the serum concentrations of ceftriaxone at various post-natal ages after ceftriaxone intravenous administration of 20 mg/kg per day. The serum concentrations of ceftriaxone at various sampling times are summarized in **Table.4**. In neonates, the proportion of extracellular fluid is large and the amount of plasma protein is small. In addition, individual birth weights, gestational ages in weeks, cardiopulmonary functions and renal excretory functions vary in infants. All of these factors should be considered when selecting the dose and administration method of a drug. In concrete terms, the distribution volume is large in neonates, which causes a low peak concentration. In addition, neonate renal excretory function is low and the hepatic enzyme system is immature, thus the half-life of drugs is prolonged in neonates. Therefore, the same dose per unit time as that for children (including infants) needs to be administered to neonates at dosing intervals that may be prolonged according to renal function (39). In neonates, the absorption of drugs administered orally varies. Therefore, in principle, antibacterial drugs are not administered orally to neonates. Other than the oral route, the routes of administration include intramuscular and subcutaneous routes. The distribution of a drug in the body is affected largely by organ and tissue blood flow, pH, intracellular and extracellular fluid volumes and their ratio, the lipophilic feature of the drug, ionization, protein binding, and membrane permeability. In fetuses, the proportion of water to body weight is large. Although the proportion decreases gradually until birth, it is 70-80% even for normal full-term neonates.

Then the proportion decreases with aging, and in infants, it is 60%, of that in adults. In general, therefore, the distribution volume is large and the maximum blood concentration of a drug is low in neonates. The drug metabolizing enzymes change markedly during neonatal maturation. In general, the hepatic enzyme system at birth is immature because the enzyme activities are low. Therefore, the metabolism and excretion of drugs are delayed in neonates. Renal excretion of drugs consists of glomerular filtration, active tubular secretion, and reabsorption from the tubular lumen to tubular cells. Many

antibacterial drugs are excreted via the kidney as unchanged compounds. Aminoglycoside antibiotics are excreted predominantly by glomerular filtration, and β-lactam antibiotics are excreted by tubular secretion. In neonates, the renal functions: renal blood flow, glomerular filtration rate, concentration ability, acid excretion ability, and maximal glucose reabsorption amount are low. Therefore, the excretion of drugs excreted via the kidneys is delayed. It is known that the glomerular filtration rate is 25 ml/min per 1.73 $m^2$ at 24 hours after normal full-term delivery, which doubles or trebles at the age of 1-13 weeks (40-43). It increases gradually in 12-24 months, and reaches the level for adults at the age of 3 years. The glomerular filtration rate is even lower in neonates with a low birth weight. Therefore, the dosing intervals should be increased in neonates.

Mean pharmacokinetic data on 40 neonates treated with 50 mg/kg/day ceftriaxone, as a single intramuscular or intravenous injection were reported by James et al. (6). Ceftriaxone concentrations were measured in heel-prick blood collected 0.25, 0.5, 1, 3, 7, 12 and 24 hours after the first dose of ceftriaxone and/or on day 3 or 4 of treatment. Blood was taken pre-, mid- and post-treatment for a full blood count, serum alanine aminotransferase, total protein, albumin, urea and creatinine estimations. The pharmacokinetic parameters of ceftriaxone are summarized in **Table.5**.

The differences in pharmacokinetic values following single or multiple doses are largely due to the higher post-natal age. Elimination half-life, trough serum concentration, and time to peak serum concentration following intramuscular administration decreased (p-value < 0.05) and clearance increased with post-natal age (p-value < 0.001). Post-natal age is the single most important factor affecting the pharmacokinetics of ceftriaxone. Gestational age alone had little effect. In comparables infants the pharmacokinetic values were the same after intravenous or intramuscular administration. Three samples of cerebrospinal fluid were collected during treatment and ranged between 2.1 and 3.8 µg/ml at times of 25 min to 22 hours post-injection. These specimens were culture-negative and did not contain an excess of leukocytes. None of the infants studied was found to have antibiotic-associated clotting defects and the incidence of loose stools was no higher in the study group than in infants not receiving ceftriaxone. There is now considerable evidence that ceftriaxone is effective for the treatment of meningitis in children (37, 44-47).

During or immediately after treatment, 6 infants were found to be colonized with faecal streptococci, and 7 with Pseudomonas aeruginosa. None of these infants showed signs of infection and no attempt was made to eradicate the organisms. Five infants who harbored Candida albicans post-treatment received nystatin. There was no evidence that organisms acquired resistance during treatment with ceftriaxone. Three very sick infants also received ceftriaxone for 5 days because of a strong clinical suspicion of infection. There were 38 infants with various clinical signs and symptoms suggestive of infection on primary assessment but who had negative bacteriological cultures. Since they showed significant clinical improvement, ceftriaxone therapy was stopped after 48 hours. Treatment of 9 infants was changed from ceftriaxone to gentamicin plus penicillin or ampicillin because of general clinical deterioration. No adverse clinical side-effects of ceftriaxone therapy were noted. Detailed biochemical analysis of the 40 infants in the pharmacokinetic study group and routine biochemical investigations indicated that ceftriaxone

therapy was not associated with any significant adverse changes in renal or hepatic function. Ceftriaxone pharmacokinetics were determined in 26 newborn infants after a single intravenous dose of 50 mg/kg. Multiple doses of 50 mg/kg were given every 12 hours to 14 infants, 5 of whom received some doses intramuscularly. Blood samples were obtained from each of the 26 infants by heel-stick technique just before the ceftriaxone dose and at 0 time (end of infusion), 0.5, 1, 2, 4, and 6 hours after infusion (48). Ceftriaxone pharmacokinetics were calculated with values obtained from 0.5 to 6 hours after the dose was administrated and assuming a one-compartment model.

Plasma concentration and pharmacokinetic values in 26 newborn infants aged 1 to 45 days were categorized by birth weight and chronological age groups and shown in **Table.6**. The largest plasma concentrations were observed at completion of the 15 min infusion (0 time) and the mean values ranged from 136 to 173 µg/ml. The mean plasma half-life values were longest (7.7 to 8.4 hours) in infants weighing ≤ 1,500 grams at birth, as compared with values (5.2 to 7.4 hours) in those weighing > 1.500 grams. The shortest half-life values (4.8 and 3.5 hours) were noted in the two oldest infants, aged 33 and 45 days, respectively. The mean distribution volume values ranged from 0.497 to 0.608 l/kg and were not associated with differences in the various neonates. The mean plasma clearance values were similar for the four study groups. Of 9 infants who received multiple ceftriaxone doses intravenously every 12 hours for 4 to 9 days, 5 showed evidence of drug accumulation. Ceftriaxone concentrations in randomly collected urine samples ranged from 113 to 3,350 µg/ml (median, 618 µg/ml). Ceftriaxone was well tolerated, and there was no evidence of hematological or hepatic toxicity after multiple doses. These pharmacokinetic data are consistent with the view that ceftriaxone can most likely be administered once daily to newborn infants who have suspected or proven bacterial diseases. Plasma concentrations should exceed the $MIC_{90}$s for group B streptococci and gram-negative enteric bacilli by at least 500-fold at 0.5 hours, 100-fold at 12 hours, and 50-fold at 24 hours after a single dose of 50 mg/kg ceftriaxone (35, 49). Seven neonates and 7 infants ranging in age from 9 to 30 days and from 3 to 9 months, respectively, received intravenous single daily doses of ceftriaxone for treatment of purulent meningitis. Newborn and preterm infants, with a post-natal age < 14 days, received 50 mg/kg ceftriaxone every 24 hours, whereas 100 mg/kg of ceftriaxone was given to the older neonates and infants (50). Serial blood samples were collected through central or peripheral venous catheters immediately after dosing and 1, 4, 8, 12, 18, and 24 hours after termination of the infusions.

Repeated lumber punctures were performed in all 14 children with purulent meningitis at 4 and 24 hours after the first dose of ceftriaxone. The neonates were divided into two groups, group 1 containing the neonates younger than 1 week, and group 2 those older than 1 week. Comparing the mean values between both neonatal groups as well as older infants using the Mann-Whitney rank sum test, a significant difference in clearance (p-value < 0.01) and half-life (p-value < 0.05) was observed between neonates in group 1 (clearance: 0.368 ml/min/kg, half-life: 16.2 hours) and neonates in group 2 (clearance 0.768 ml/min/kg, half-life: 9.2 hours). In infants, the clearance and half-life were 1.03 ml/min/kg and 7.1 hours, respectively. No significant differences in clearance and half-life were seen between neonates in group 2 and infants. Distribution volume at

steady-state ranged from 0.19 to 0.62 l/kg and never reached the level of significance between the 3 groups. Because ceftriaxone exhibits concentration-dependent protein binding (51), the total plasma concentration will not exactly double on doubling the dose. The respective mean ± standard deviation (SD) values of the dose-corrected plasma concentrations for neonates in groups 1 and 2 were 124±14 µg/ml and 108±11 µg/ml, respectively, at 1 to 2 hours, 59±3 µg/ml and 36±12 µg/ml, respectively, at 12 hours, and 34±16 µg/ml and 15±7 µg/ml, respectively, at 24 hours after dosing. The concentrations for the infants were 212±33 µg/ml at 1-2 hours; 49±39 µ/ml at 12 hours, and 13±15 µg/ml at 24 hours. The ceftriaxone concentrations in the cerebrospinal fluid, the areas under the cerebrospinal fluid concentration versus time, and the area ratios (cerebrospinal fluid/plasma concentrations of ceftriaxone) in neonates and infants with bacterial and aseptic meningitis are summarized in table 7. There was a significant difference (rank sum test) in the percentage of penetration of ceftriaxone into the cerebrospinal fluid (17.0% versus 4.1%) calculated as the area ratio (cerebrospinal fluid/plasma concentrations) when patients with bacterial and aseptic meningitis were compared (**Table.7**).

In infants, the average renal clearance of ceftriaxone was 0.485 ml/min/kg and accounted for 47.1% of total body clearance. In groups 1 and 2, the average of renal clearance of ceftriaxone was 0.282 ml/min/kg and 0.539 ml/min/kg, respectively, (p-value < 0.05) and represented 77% and 70% of the respective total body clearance values. The percent of total body clearance values (accounted for by renal clearance) between neonates and infants were statistical significant (p-value < 0.05, Mann-Whitney rank test). However, no significant differences could be shown for renal clearance in the three groups. The average half-life in neonates younger than 7 days post-natal age was significantly longer (16.2 hours) than that in older neonates (9.2 hours) and infants (7.1 hours). Martin (52, 53) observed that 97% of children with purulent meningitis had a satisfactory bacteriologic response. Based on these results, the long half-life, and the good cerebrospinal fluid penetration of ceftriaxone, combined with the efficacy and safety of this drug, a regimen of 50 to 100 mg/kg/24 hours (4 grams maximum) for the treatment of serious infections, including meningitis, seems appropriate.

## 4- DISCUSSION

Ceftriaxone is a versatile and useful "third-generation" cephalosporin that only needs to be given once a day (Neonatal Formulary). Ceftriaxone, like other cephalosporins, kills bacteria by interfering with the synthesis of cell walls (2). This antibiotic displaces bilirubin from albumin binding sites and thus increases the unconjugated free bilirubin in plasma. Ceftriaxone should not be given to infants with plasma hyperbilirubinemia (1). Ceftriaxone is a β-lactamase-resistant cephalosporin that is active, like cefotaxime and ceftazidime, against some important gram-positive and most gram-negative bacteria. Experimental and clinical studies have demonstrated that ceftriaxone is a broad-spectrum β-lactamase-resistant cephalosporin, active against both aerobic and anaerobic gram-positive and gram negative pathogens (7-9). Ceftriaxone has a broad spectrum of activity and improved β-lactamase stability (5). The $MIC_{90}$s of ceftriaxone range from 0.06 µg/ml and 2 µg/ml and are 0.1 µg/ml (Escherichia coli), 0.1 µg/ml (Klebsiella species), 0.2 µg/ml (Proteus species), 0.3 µg/ml (Enterobacter species), 0.4 µg/ml (Serratia species), 0.06 µg/ml (Streptococcus agalactiae), and 2 µg/ml (Staphylococcus aureus, β-lactamase

producers) (3). After a single intravenous dose of 50 mg/kg ceftriaxone to 26 neonates, the highest concentrations were observed at completion of 15 min of infusion (0 time) and ranged from 136±8.9 and 173±23 µg/ml, and 6 hours after administration, ceftriaxone concentrations ranged from 66±3.3 and 74±5.4 µg/ml (48). These values exceed the $MIC_{90}$s for various pathogens present in the neonatal ward. Because of good cerebrospinal fluid penetration, even when the meninges are not inflamed, ceftriaxone 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 **c**hloramphenicol, and to treat gonorrhea (Neisseria gonorrhea infection) (1).

The high prolonged plasma half-life of ceftriaxone and its good penetration in meninges is useful in the treatment of meningitis sustained by susceptible bacteria (4). There is now considerable evidence that ceftriaxone is effective for the treatment of meningitis in children (44-47). The concentration of ceftriaxone was measured in the lumbar cerebrospinal fluid of 3 neonates with not-inflamed meninges and ranged from 2.1 and 3.8 µg/ml, at times ranging from 25 min to 22 hours. Elimination half-life and trough serum concentration decrease and the clearance increases with increasing the post-natal age (6). Post-natal age was the single most significant factor affecting pharmacokinetics. Ceftriaxone is a safe, well tolerated antibiotic, and effecting alternative to conventional therapy for infected neonates. Prolonged therapy is associated with superficial colonization with inherited resistant bacteria. In neonates, the proportion of extracellular fluid is large and the amount of plasma protein is low. In addition, individual birth weights, gestational ages in weeks, cardiopulmonary functions and renal excretory functions vary in infants. The distribution volume is large in neonates, which causes a low peak concentration. In addition, neonatal renal excretory function is low and the hepatic enzymes are immature, thus the half-life of drugs is prolonged in neonates (39). McCracken et al. (48) observed that the ceftriaxone plasma half-life values were longest (7.7 to 8.4 hours) in infants weighing ≤ 1,500 grams at birth, as compared with values (5.2 to 7.4 hours) in those weighing > 1,500 grams. The shortest half-life values (4.8 and 3.5 hours) were noted in the two oldest infants aged 33 and 45 days, respectively.

The World Health Organization first-line recommended penicillin and gentamicin for treating bacterial meningitis in young infants. Swann et al. (22) identified 259 culture-positive isolates from 259 infants ≤ 2 months of age. Sixty isolates were from neonates ≤ 7 days old, in whom the most common pathogens were group B Streptococcus (27/60; 45.0%), Streptococcus pneumoniae (13/60; 21.7%) and nontyphoidal Salmonella enterica (7/60; 11.7%). Isolates were more susceptible to ceftriaxone than to the combination of penicillin and gentamicin (218/220; 99.1% versus 202/220; 91.8%, Fisher's exact test, p-value = 0.006). Penicillin and gentamicin provide less coverage for gram-negative than gram-positive isolates (74/86; 86.0% versus 155/163; 95.1%, r = 6.24, p-value = 0.012). Ceftriaxone is an active agent in the treatment of meningitis sustained by gram-positive and gram-negative bacteria.

Ceftriaxone was administered as a single or multiple intravenous or intramuscular injection of 50 mg/kg dose to 39 neonates (4). After intramuscular ceftriaxone administration, its concentrations were higher in the first 2-3 hours of dosage. Serum concentrations/time of ceftriaxone

curve declined more rapidly than following the first injection because the half-life of ceftriaxone decreased (p-value < 0.001) and the clearance increased (p-value < 0.0002) with increasing post-natal age. There was no significant difference in peak ceftriaxone concentration following intravenous or intramuscular administration. Older neonates exhibited lower trough plasma concentrations (p-value < 0.01) and shorter half-lives (p-value < 0.01). Elimination half-life and trough serum concentration decreased and the clearance increased with increasing the post-natal age (6). Post-natal age was the single most significant factor affecting pharmacokinetics. Ceftriaxone is a safe and effective alternative to conventional therapy for infected neonates. Prolonged therapy is associated with superficial colonization with inherited resistant bacteria. Ceftriaxone is excreted unaltered almost equally in the bile and urine, so treatment does not require adjustment unless there are both renal and hepatic failures. This antibiotic has a longer half-life than other cephalosporins and is 15 hours at birth and 7 hours over some 2 to 4 weeks. Ceftriaxone crosses the placenta and appears in the amniotic fluid, but there is no evidence of teratogenicity in animals, but only limited information regarding its safety during human pregnancy is available (1). Ceftriaxone is used to treat gonorrhea, an intramuscular injection of 250 mg ceftriaxone is used to treat this disease. Neonatal gonococcal eye infection is treated with a single intramuscular dose of 125 mg ceftriaxone (1). There is an interaction between ceftriaxone and calcium. Never give ceftriaxone intravenously to any child who is being, or who has recently received solutions containing calcium. Precipitation could be potentially lethal. Use cefotaxime instead. The concurrent use of intravenous ceftriaxone and calcium-containing solutions in the newborn and infant may result in a life-threatening adverse drug reaction (10). Citrobacter meningitis is an uncommon enteric gram-negative infection in neonates and young infants. Approximately 30% of children infected by Citrobacter freundii die. Empiric therapy with ampicillin 225 mg every 12 hours and gentamicin 11 mg every 8 hours did not eradicate the infection. A therapy of 250 mg of ceftriaxone every 12 hours for 9 days was found to be successful in the eradication of Citrobacter freundii (15).

Steele and Bradsher (45) evaluated the efficacy and safety of ceftriaxone in 30 pediatric and 12 young adult patients with serious infections. Ceftriaxone was administered intravenously to children at a dose of 50 to 75 mg/kg/day in two divided doses. Those with central nervous system infections received 100 mg/kg/day. The diseases treated included pneumonia, sepsis, ventriculoperitoneal shunt infections, osteomyelitis, brain abscesses, and peritonitis. Clinical cures were achieved in all cases. Ceftriaxone appears to represent an important alternative to therapy. A total of 190 respiratory pneumococcal isolates obtained from children aged from 0 to 14 years were treated with ampicillin or ceftriaxone (24). The minimal amoxicillin concentrations inhibiting the growth of 50% and 90% isolates were 0.50 µg/ml and 1.0 µg/ml, respectively, and the minimal ceftriaxone concentrations inhibiting the growth of 50% and 90% isolates were 0.25 µg/ml and 50 µg/ml, respectively. Ceftriaxone is more potent than amoxicillin in inhibiting respiratory pneumococcal infection.

Steele et al. (31) studied the pharmacokinetics of ceftriaxone in 5 full-term neonates 8 to 21 days old and 25 infants aged between 6 weeks to 2 years. The study was randomized and half the patients received 50 mg/kg and the other half received 75 mg/kg. Results for five neonates, all over 7 days of life, were not different from those for older infants, so determinations were combined for

analysis. Peak concentrations of ceftriaxone were 230±64 µg/ml and 295±76 µg/ml after ceftriaxone doses of 50 mg/kg and 75 mg/kg, respectively. The concentrations of ceftriaxone in a sample of cerebrospinal fluid was 5.4 µg/ml (dose of 50 mg/kg) and 6.4 µg/ml (dose of 75 mg/mg). These cerebrospinal fluid concentrations exceeded the $MIC_{90}$s for common pathogens by at least 10-fold. Seven neonates and 7 infants ranging in age from 9 to 30 days received a single intravenous dose of ceftriaxone for 6 to 10 days. The doses of ceftriaxone were 50 mg/kg and 100 mg/kg for neonates < 14 days of post-natal age and for older neonates, respectively (50). The mean plasma half-life and clearance values were 16.2 hours and 0.368 ml/min/kg, respectively, in younger neonates, and 9.2 hours and 0.768 ml/min/kg, respectively, in older neonates.

The levels of significance for younger and older neonates were <0.05 and 0.01 in the half-life and clearance, respectively. In infants, the half-life and clearance values were 7.1 hours and 1.03 ml/min/kg, respectively. The distribution volumes at steady-state were not different in younger, older neonates, and infants, and ranged from 0.19 to 0.62 l/kg. In infants, the average renal clearance was 0.485 ml/min/kg and accounted for 47.1% of total body clearance, whereas the values of 0.282 ml/min/kg and 0.539 ml/min/kg (p-value < 0.05) were observed in young and old neonates, respectively. The respective renal clearance accounted for 77% and 70%, of the respective total body clearance. The mean ± SD values of the dose-corrected plasma concentrations for younger and older neonates were respectively 124±14 µg/ml and 108±11, respectively, at 1 to 2 hours, and 59±3 and 36.12 µg/ml, respectively, at 12 hours. Martin (52, 53) observed that 97% children with purulent meningitis had a satisfactory bacteriologic response when treated with ceftriaxone. The long half-life, and the good penetration into the cerebrospinal fluid of ceftriaxone, combined with the efficacy and safety of this drug, indicate drug a regimen of 50 to 100 mg/kg/24 hours for the treatment of serious infections, including meningitis, is appropriate. In conclusion, ceftriaxone is a versatile and useful "third generation" β-lactamase-resistant cephalosporin with a long half-life (15 hours, at birth). The long half-life and the good penetration in the cerebrospinal fluid, ceftriaxone is a useful antibiotic to treat meningitis in neonates and infants. Ceftriaxone is active against Escherichia coli, Klebsiella species, Enterobacter Species, Serratia species, Streptococcus agalactiae, Streptococcus pyogenes, Staphylococcus aureus, and Homophiles influenzae. After a single daily intravenous dose of 50 mg/kg or 75 mg/kg ceftriaxone, the peak plasma concentrations of this antibiotic are 230±64 and 295±76 µg/ml, respectively, and 24 hours after the administration of 50 mg/kg ceftriaxone the plasma concentrations are 55±23 µg/ml.

The $MIC_{90}$s of ceftriaxone for most major neonate bacteria are extremely low when compared with attainable serum concentrations of this antibiotic, e.g. Escherichia coli ($MIC_{90}$ = 0.1 µg/ml), Klebsiella species ($MIC_{90}$ = 0.1 µg/ml), Proteus species ($MIC_{90}$ = 0.2 µg/ml), Enterobacter species ($MIC_{90}$ = 0.3 µg/ml), Serratia species ($MIC_{90}$ = 0.4 µg/ml), Streptococcus agalactiae ($MIC_{90}$ = 0.06 µg/ml) and Staphylococcus aureus (β-lactamase producers) ($MIC_{90}$ = 2 µg/ml). Thus, after 24 hours of the administration of 50 mg/kg, the ceftriaxone concentrations exceed the MICs for most of the important bacteria. Ceftriaxone is used to treat gonococcal infection. This antibiotic displaces bilirubin from albumin binding sites, increasing the unconjugated bilirubin in plasma, and developing bilirubin encephalopathy. Thus ceftriaxone

should not be administered to infants with hyperbilirubinemia. There is an interaction between ceftriaxone and calcium, this interaction may be lethal and solutions containing calcium should not be administered to infants treated with ceftriaxone. The World Health Organization suggests the use of penicillin and gentamicin for treatment of meningitis in infants. However, ceftriaxone has been found to be more effective than the combination of penicillin and gentamicin in the treatment of meningitis in infants. Ceftriaxone is a safe, well tolerated antibiotic, and effective agent for the treatment of serious infections, including meningitis, in neonates and infants.

## 5- CONCLUSIONS

For the first time, the present meta-analysis aimed to employ an analytic approach to gather information on the diagnostic value of plasma/serum NGAL concentration in detection of AKI in children. The results of the study indicated that measuring the plasma level of NGAL in the first 12 hours after admission or surgery while considering a cut-off level of 100 mg/dL provides the best prognostic performance for detection of AKI in children. The high diagnostic value of this biomarker in the first hours after admission is one of the strengths of this method and increases its applicability in the clinical settings.

## 6- CONFLICT OF INTEREST

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.

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**Table-1**: Ceftriaxone pharmacokinetic parameters in infants and children. Ceftriaxone was administered intravenously.

| Dose (mg/kg) | Half-life (hours | Clearance ml/h/kg | Distribution volume (ml/kg) | Peak concentration (µg/ml) |
|---|---|---|---|---|
| 50 | 5.8±2.8 | 51±24 | 382±129 | 230±64 |
| 75 | 5.4±2.1 | 55±18 | 387±56 | 295±76 |

The figures are the mean±SD, by Steele et al. (31).

**Table-2**: Mean±SD plasma ceftriaxone concentrations (µg/ml) following intravenous and intramuscular administration of 50 mg/kg ceftriaxone, by Mulhall et al. (4).

| Doses | Sub-group | | Time after ceftriaxone administration (hours) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Status | Number of cases | 0.25 | 0.5 | 1 | 3 | 7 | 12 | 24 |
| First dose | IM | 6 | 67±16 | 110±47 | 120±32 | 143±19 | 128±28 | 89±21 | 54±19 |
| | IV | 12 | 155±41 | 150±40 | 147±47 | 138±32 | 110±34 | 87±37 | 55±23 |
| Multiple doses | IM | 18 | 119±34 | 142±24 | 161±32 | 155±33 | 115±28 | 82±27 | 33±15 |
| | IV | 13 | 172±32 | 171±33 | 162±35 | 132±28 | 88±27 | 63±23 | 32±14 |

IM: intramuscular administration, IV: intravenous administration, SD: standard deviation.

**Table-3**: Plasma pharmacokinetic parameters of ceftriaxone in 39 neonates after single or multiple intravenous or intramuscular 50 mg/kg ceftriaxone administration. The figures are the mean ± SD and range, by Mulhall et al. (4).

| Variables | Single dose | | Multiple doses | |
|---|---|---|---|---|
| | Intravenous administration (N=12) | Intramuscular administration (N=6) | Intravenous administration (N=10) | Intramuscular administration (N=15) |
| Peak plasma concentration (µg/ml) | 153±39 (0.115-236) | 141±19 (123-175) | 134±25 (95-179) | 143±23 (134-212) |
| Trough plasma concentration (µg/ml) | 54±22 (18-96) | 51±21 (25-84) | 21.6±6.0 (13-31) | 25±5.5 (18-49) |
| Serum elimination half-life (hours) | 15.4±5.6 (8.8-29) | 15.8±5.8 (10.6-23.4) | 8.5±1.5 (6.1-11.2) | 9.7±2.2 (6.9-16.4) |
| Total body clearance (ml/min/kg) | 0.28±0.12 (0.16-0.61) | 0.28±0.13 (0.5-0.40) | 0.54±0.11 (0.17-0.65) | 0.41±0.11 (0.19-0.58) |
| Distribution volume (ml/kg) | 326±70 (211-434) | 323±38 (265-376) | 393±75 (278-527 | 321±52 (235-401) |
| Time to peak plasma concentration (hours) | ____ | 1.8±0.8 (0.8-3.2) | ___ | 1.4±0.7 (0.2-2.8) |

N = number of cases.

**Table-4**: Serum concentrations of ceftriaxone (µg/ml) in neonates at different post-natal ages and at various sampling times. Ceftriaxone was administered intravenously at the dose of 20 mg/kg per day. The figures are the mean, by Sato (39).

| | Sampling times | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age (days) | 5 min | 15 min | 30 min | 1 hour | 2 hours | 4 hours | 6 hours | 8 hours | 12 hours | 24 hours |
| 0 (N=3) | ___ | 90.12 | 87.51 | 61.73 | 39.85 | 31.25 | 32.82 | 29.69 | 28.13 | 23.44 |
| 1 (N=5) | 100.0 | 80.49 | 67.97 | 46.10 | 38.55 | 32.04 | 29.30 | 22.66 | 24.81 | 18.66 |
| 2 (N=5) | 104.70 | 73.96 | 67.19 | 54.69 | 53.13 | 43.75 | 35.16 | 32.82 | 28.13 | 12.11 |
| 3 (N=5) | 119.81 | 89.08 | 78.13 | 64.07 | 52.35 | 42.97 | 36.72 | 27.35 | 21.88 | 12.66 |
| 4 (N=4) | 122.93 | 71.89 | 60.95 | 45.32 | 34.38 | 29.70 | 24.61 | 21.10 | 19.15 | 13.28 |
| 5 (N=5) | 133.34 | 62.50 | 48.44 | 42.19 | 37.50 | ___ | 26.57 | 23.44 | 20.32 | 14.22 |
| 6 (N=3) | 139.57 | 106.26 | 93.76 | 75.00 | 56.25 | 43.75 | 39.07 | 34.38 | 31.25 | 16.67 |

N = number of cases.

**Table-5**: Plasma pharmacokinetic parameters of ceftriaxone in 40 neonates. Ceftriaxone was administrated intravenously or intramuscularly at the dose of 50 mg/kg per day. The figures are the mean±SD, by James et al. (6).

| Parameters | Single dose | Multiple doses |
|---|---|---|
| Peak plasma concentration (µg/ml) | 149±33 | 141±45 |
| Trough plasma concentration (µg/ml) | 54±21 | 25±9.5 |
| Serum elimination half-life (hours) | 15.5±5.4 | 9.4±2.5 |
| Total body clearance (ml/min/kg) | 0.28±0.13 | 0.45±0.15 |
| Distribution volume (ml/kg) | 325±59 | 348±72 |

**Table-6**: Plasma concentrations and ceftriaxone pharmacokinetic parameters in 26 newborn infants. Ceftriaxone was administered intravenously at the dose of 50 mg/kg per day. The figures are the mean±SEM, by McCracken et al. (48).

| Variables | | Number of cases | Mean plasma ceftriaxone concentrations (µg/ml) at following time (hours) | | | | | | Half-life (hours) | Distribution volume (l/kg) | Plasma clearance (ml/min) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean weight at birth (grams) | Mean age (days) | | 0 | 0.5 | 1 | 2 | 4 | 6 | | | |
| 1,164 | 3.2 | 10 | 145±18 | 99±3.3 | 91±3.3 | 80±3.9 | 70±2.9 | 66±3.3 | 7.7±0.6 | 0.61±0.02 | 1.0±0.2 |
| 1,176 | 6.7 | 3 | 136±8.9 | 120±17 | 108±8.4 | 91±1.8 | 76±1.5 | 71±4.4 | 8.4±1.6 | 0.53±0.03 | 0.73±0.1 |
| 2,670 | 2.8 | 9 | 158±9.1 | 118±8.6 | 112±7.3 | 108±8.4 | 79±7.1 | 74±5.4 | 7.4±0.5 | 0.52±0.04 | 1.8±0.2 |
| 2,112 | 22.5 | 4 | 173±23 | 128±5 | 116±7 | 112±9 | 86±9 | 67±12 | 5.2±0.6 | 0.50±50 | 1.6±0.1 |

**Table-7**: Individual cerebrospinal fluid ceftriaxone concentrations (µg/ml), areas under the cerebrospinal fluid (AUC) versus time curves, and area ratios (cerebrospinal fluid/plasma ceftriaxone concentrations) in neonates and infants with bacterial and aseptic meningitis, by Martin et al. (50).

| Status | Patient age | Dose (mg/kg) | Conc. at 4 hours | Conc. at 12 hours | Conc. at 24 hours | AUC (µg/ml/hour) | Area ratio (%) |
|---|---|---|---|---|---|---|---|
| Bacterial meningitis | 27 days | 100 | 31.6 | 57.8 * | --- | --- | --- |
| | 20 days | 50 | 14.6 | 7.2 | 2.2 | 195 | 14.9 |
| | 24 days | 144 | 24.5 | 9.5 | 4.2 | 390 | 13.7 |
| | 10 days | 50 | 5.0 | 13.4 | 3.3 | 175 | 13.0 |
| | 9 days | 50 | 22.0 | --- | 3.4 | 321 | 94.1 ** |
| | 6.0 months | 100 | 25.0 | 12.7 | 4.5 | 395 | 32.2 |
| | 9.0 months | 114 | 15.4 | 4.8 | 17 | 168 | 14.2 |
| | 6.0 months | 100 | 21.1 | --- | 2.0 | 279 | 24.5 |
| | 8.5 months | 100 | 5.6 | 3.2 | 1.4 | 84 | 6.4 |
| Group average | --- | --- | 18.3 | 8.5 | 2.8 | 251 | 17.0 |
| Aseptic meningitis | 16 days | 100 | 8.5 | --- | 3.2 | 192 | 6.5 |
| | 30 days | 100 | 5.9 | --- | 2.1 | 130 | 6.3 |
| | 3.0 months | 93 | 2.0 | --- | 0.5 | 44 | 2.5 |
| | 7.0 months | 100 | 2.8 | 2.0 | 1.1 | 55 | 2.5 |
| | 9.0 months | 100 | 3.0 | --- | 1.9 | 95 | 2.5 |
| Group average | --- | --- | 4.4 | --- | 1.8 | 103 | 4.1 |

Conc = Ceftriaxone concentration (µg/ml). *Died of circulatory shock after 12 hours; sample taken immediately post-mortem; not included in mean. **Died after 5 days of treatment; not included in mean.