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Clinical Pharmacology of Cefotaxime in Neonates and Infants: Effects and Pharmacokinetics

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Abstract

Cefotaxime is a bactericidal "third generation" cephalosporin has a broad-spectrum activity against gram-positive microorganisms and exceptional activity against most gram-negative microorganisms. Cefotaxime is widely considered to be the antibiotic of choice for the management of neonatal meningitis and sepsis caused by gram-negative bacteria. Cefotaxime is active against Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella specimens, Staphylococcus, Enterobacter species, Haemophilus parainfluenzae, Pseudomonas aeruginosa, Escherichia coli, Citrobacter freundii, and Klebsiella pneumoniae. In neonates, the recommended dose of cefotaxime is 25 mg/kg every 6 hours by intravenous or intramuscular administration. Some authors administered cefotaxime at a daily dose of 150 or 300 mg/kg.

After the intravenous administration of 50 mg/kg cefotaxime every 6 hours, the serum concentrations of this antibiotic are 56.9±28.7 µg/ml at 1 hour and 3.66±5.65 µg/ml at 6 hours after the administration. The cerebrospinal fluid concentration of cefotaxime, measured 1 hour after the intravenous administration of 50 mg/kg cefotaxime, is 3.72±5.57 µg/ml. The MIC_{50} (µg/ml), and the MBC_{50} (µg/ml) are 0.024±0.026 and 0.064±0.054, respectively, for Haemophilus influenzae, 0.062±0.034, and 0.240±0.027, respectively, for Streptococcus pneumoniae and 0.057±0.088, and 0.283±0.44, respectively, for Neisseria meningitis. In neonates, the half-life of cefotaxime is 2 to 6 hours, it varies with gestational and postnatal ages, and the clearance and distribution volume are 0.074±0.03 l/h/kg, and 0.461±0.027 l/kg, respectively. Cefotaxime diffuses in tissues and penetrates into the cerebrospinal fluid. This antibiotic is safe and well tolerated in neonates. The aim of this study was to review the effects and pharmacokinetics of cefotaxime in neonates and infants.

Key Words: Cefotaxime, Effects, Neonate, Pharmacokinetics, Resistance, Susceptibility.

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1-INTRODUCTION

Cefotaxime is a bactericidal "third generation" cephalosporin, has a broad-spectrum activity against gram-positive microorganism and exceptional activity against most gram-negative microorganisms. Cefotaxime is widely considered to be the antibiotic of choice for the management of neonatal meningitis and sepsis caused by gram-negative bacteria. The tissue diffusion and the penetration into the cerebrospinal fluid of cefotaxime are good. In neonates, the half-life is 2 to 6 hours and varies with gestational age and with postnatal age. The "third generation" cephalosporins, such as cefotaxime, should be limited to the management of proven gram-negative meningitis and septicemia. Several units have reported the emergence of resistant strains of Enterobacter cloacae when cefotaxime is used regularly in the first-line managements of neonatal meningitis and sepsis caused by coagulase-negative staphylococcal infection (1).

Cefotaxime, like other cephalosporins kills bacteria by interfering with synthesis of their cell walls. They are most commonly used in hospitalized patients for prophylaxis because of their broad spectrum of activity. The "third generation" cephalosporins are most useful when treating aerobic gram-negative bacteria causing meningitis, sepsis and biliary tract infections. They should not be used as a monotherapy to treat mixed infections or as an empirical therapy for serious bacterial infections when staphylococci, streptococci, or anaerobes might be the etiologic agents (2).

The minimum inhibitory concentrations (MICs) for Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella specimens, Staphylococcus, Enterobacter species, and Haemophilus parainfluenzae, Pseudomonas aeruginosa, Escherichia coli, Citrobacter freundii, and Klebsiella pneumoniae range from 0.01 µg/ml to 0.50 µg/ml (3). After the intravenous administration of 50 mg/kg cefotaxime every 6 hours, the mean serum cefotaxime concentration, on the second day of therapy, is 56.9$\pm$28.7 µg/ml at 1 hour and 3.66$\pm$5.65 µg/ml at 6 hours after administration of this drug. The cerebrospinal fluid concentrations of cefotaxime measured 1 hour after drug administration of 50 mg/kg cefotaxime is 3.72$\pm$5.57 µg/ml (4). Therefore, the concentration of cefotaxime at 6 hours from administration of 50 mg/kg is many times higher than the MIC values of important bacteria.

One hundred and eighty-seven children affected by bacterial meningitis were treated intravenously at daily doses of 150 to 300 mg/kg cefotaxime (3). The causative microorganisms were Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, enteric gram-negative bacilli, and Staphylococcus species. The sterilization of the cerebrospinal fluid was achieved in the first 72 hours of treatment in 90.1% of patients. One hundred and seventy-two patients (92.0%) were cured. Cefotaxime is an effective, safe and well tolerated antibiotic for the treatment of childhood bacterial meningitis and sepsis.

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, EMBASE, Google scholar and PubMed as search engines; July 2017 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

The following key words "cefotaxime dosage neonates", "cefotaxime effects neonates", "cefotaxime meningitis neonates", "cefotaxime susceptibility

neonates", "cefotaxime resistance neonates" and "cefotaxime pharmacokinetics neonates", were used. In addition, the books Neonatal Formulary (1), and NEOFAX by Young and Mangum (5) were consulted.

3-RESULTS

3-1. Uses of cefotaxime

Treatment of neonatal meningitis and sepsis caused by susceptible gram-negative organisms such as: Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella specimens, Staphylococcus, Enterobacter specimens, and Haemophilus parainfluenzae, Pseudomonas aeruginosa, Escherichia coli, Citrobacter freundii, and Klebsiella pneumoniae (5).

3-2. Doses of cefotaxime in neonates and infants

3-2-1. Gonococcal infections

Give 25 mg/kg cefotaxime intravenously per dose over 30 min infusion or intramuscularly (5).

3-2-2. Gonococcal ophthalmia prophylaxis in newborns whose mother have gonorrhea at the time of delivery

Give 100 mg/kg intravenously cefotaxime over 30 min infusion or intramuscularly (5). Leroux et al. (6) conducted a population pharmacokinetic study of cefotaxime in neonates and young infants in order to evaluate and optimize the dosing regimen. The pharmacokinetic data from 100 neonates (gestational age ranged: 23 to 42 weeks), were modeled with an allometric two-compartment model with first-order elimination. The median values for clearance and volume of distribution at steady state were 0.12 liter/h/kg and 0.64 liter/kg, respectively. The covariate analysis showed that current weight, gestational and postnatal ages had significant impacts on cefotaxime pharmacokinetics. A model-based dosing regimen of 50 mg/kg twice a day to four times a day, according to gestational and postnatal ages, was established. The associated risk of overdose for the proposed dosing regimen was 0.01%.

The median MIC values of cefotaxime for Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitis were 0.01, 0.01, and 0.004µg/ml, respectively. The intravenous dose of cefotaxime was 50 mg/kg 6 hourly. The lowest cerebrospinal fluid was 0.45µg/ml, and was 45 times higher than the MIC values of cefotaxime for Streptococcus pneumoniae and Haemophilus influenzae. The highest levels of cefotaxime in the cerebrospinal fluid ranged from 24 and 35µg/ml and were up to 8,750 times the MIC patient's causative agent. A wide range of cefotaxime concentration in the cerebrospinal fluid ranged considerably. Levels varied with post-dose interval and duration of illness (7).

Cefotaxime has received wide acceptance as a first-line antibiotic for many infections in neonates, infants and children (8). With an average elimination half-life of about 1 hour, cefotaxime is not considered to be a "long-half-life cephalosporin" like ceftriaxone. For this reason, currently accepted dosage regimens for cefotaxime in infants and children employ a dosage of 50 mg/kg every 6 hours. Cefotaxime dosing may be 75 mg/kg every 8 hours or every 12 hours. At this dosage, cefotaxime serum concentrations are adequate to effectively kill many of the common pathogens against which the drug is currently indicated for use in children. It would appear, therefore, that increasing the cefotaxime dosage to 75 mg/kg administered at 8 hour intervals would result in less frequent drug administration which would not be expected to compromise safety and efficacy.

Nine neonates with culture proved gonococcal ophthalmia neonatorum were treated with a single intramuscular

injection of 100 mg/kg cefotaxime without topical antibiotic therapy (9). Five of the nine strains were penicillinase-producing Neisseria gonorrhea. All nine cases were clinically and microbiologically cured, and no side effects were observed.

3-3. Effects of cefotaxime and other antibiotics in neonates and infants

The in vitro effects of cefotaxime on the production of interleukin (IL)-1 beta, IL-2, IL-6, and tumor necrosis factor α were studied in term neonates and were compared with those in adults (10). The addition of cefotaxime caused a significant enhancement of IL-2 production by cells of both adults and neonates, and increased the secretion of tumor necrosis factor α by peripheral blood mononuclear cells of adults, whereas the synthesis of this cytokine by cord blood mononuclear cells of newborns was not affected. In contrast with the described stimulatory effects of cefotaxime, this drug induced dose-depended inhibition of the spontaneous and lipopolysaccharide-induced IL-1 β production by cells of the two groups, but had no effect on the in vitro production of IL-6. These data suggest that cefotaxime, apart from its known antimicrobial activity, may modify the host immune response of both newborns and adults, via the alteration of cytokine production.

Early-onset sepsis remains a serious common problem for neonates, especially preterm infants. Group B streptococcus is the most common etiologic agent, while Escherichia coli are the most common cause of mortality (11). The diagnosis of neonatal sepsis is based on a combination of clinical presentation; the use of nonspecific markers, including C-reactive protein and procalcitonin (where available); blood cultures; and the use of molecular methods, including Polymerase chain reaction (PCR). Cytokine, including interleukin 6, interleukin 8, gamma (γ) interferon, and tumor necrosis factor-α, and cell surface antigens, including soluble intercellular adhesion molecule, and Cluster of Differentiation 64 (CD64), are also being increasingly examined for use as herpes simplex virus and should be considered in the differential diagnosis.

A differential quantitative analysis was used to study the effect of cefotaxime on the fecal flora in 26 hospitalized children ranging from two days to four years of age. Fecal specimens were obtained before, during and after the therapy (12). This study was evaluated in comparison to 41 patients of the same age and from the same environment without antibiotic treatment or signs of infection. The fecal flora of the control group showed qualitative and quantitative stability. Two groups of specimens were distinguished: a group in which the upper limit was less than or equal to 10 (n = 7) (Klebsiella. Enterobacter, other enterobacteria, Staphylococcus, Pseudomonas), and a group with less than or equal to (n = 10) bacteria/g of stool (anaerobes, Escherichia coli, Streptococcus D). With cefotaxime administration there was a decrease or a disappearance in 65% of Escherichia coli and a slight decrease of Klebsiella and Enterobacter. This fact was of great interest in the treatment of endogenous secondary septicemia.

Dellagrammticas et al. (13) evaluated the clinical efficacy in terms of mortality and long-term morbidity of "third generation" cephalosporins and amikacin in combination for the treatment of gram-negative bacterial meningitis in 72 neonates without central nervous system anomalies, and with gram-negative organisms growing in their cerebrospinal fluid. All microorganism isolates were sensitive to cefotaxime or ceftazidime and to amikacin, but 80% were resistant to ampicillin. The predominant infecting microorganism was Escherichia coli (68.0%) which were sensitive to both cefotaxime and amikacin but resistant to ampicillin in 48% of cases. Survival at

discharge was 97.2%. Ventriculitis was diagnosed in 10 neonates (13.8%). Among survivors, 1 neonate (1.3%) developed hydrocephalus needing shunting and 1 neonate (1.3%) developed a brain abscess due to Proteus mirabilis with relapsed meningitis which was successfully treated with a 6-week course of chloramphenicol.

Blood and cerebrospinal fluid isolates (n = 629) from Swedish infants up to one year of age were tested in vitro against 13 antimicrobial agents in order to update the guidelines for empiric therapy of septicemia and meningitis (14). Ampicillin plus gentamicin provided inadequate empiric therapy for meningitis, due to the poor cerebrospinal fluid penetration of the aminoglycoside and the frequent occurrence of bacterial resistance to ampicillin. Ceftazidime and cefuroxime were moderately active, particularly against isolates from small infants. Cefotaxime seemed to provide the best empiric therapy of septicemia and meningitis in infants.

Two-hundred and forty-six children, aged 10 months, had multiresistant Salmonella typhimurium systemic infections (15). Of these, 220 had no metastatic focal infections and 26 had metastatic focal infections (including 12 infants with meningitis). Diarrhea and respiratory symptoms was found in 72% and fever was found in 99%. In 199 (81%) of the patients, the multiresistant Salmonella typhimurium infection was considered to be hospital-acquired. Of the 246 children, 159 were treated with cefotaxime. In this group, 16 (10.5%) patients died. However, of the 87 children who did not receive cefotaxime, 64 (74%) died. The present data confirm the high efficacy of cefotaxime in treating systemic infection with multiresistant Salmonella typhimurium.

Eighteen infants and children (1 week to 3 months of age) were treated with 200 mg/kg/day of cefotaxime for gram-negative enteric bacillary meningitis (16). Seventeen of these patients (94.4%) survived, with a complication rate of 23.5% (4/17 infants). The follow-up cerebrospinal fluid cultures at 24 hours were sterile in all infants. Cefotaxime is a safe and effective antibiotic in treating gram-negative enteric bacillary meningitis in infants and children.

A total of 236 infants were entered into the trial, of which 222 were evaluated (17). Infants were treated with cefotaxime, or penicillin plus netilmicin. The number of "definitely" and "probably" infected infants was similar in both groups and no side effects were recorded for either of the antibiotic regimens. Antibiotic sensitivity testing of bacterial isolates from peripheral sites showed almost universal sensitivity. The present results indicate that cefotaxime or netilmicin plus penicillin are suitable for the "blind" treatment of early suspected neonatal sepsis.

The activities of penicillin G, ampicillin, piperacillin, cefotaxime and ceftriaxone alone and in combination against 130 isolates of Escherichia coli, group B streptococci and Listeria monocytogenes affected by neonatal meningitis were assessed (18). Cefotaxime and ceftriaxone were highly active against Escherichia coli and B streptococci (MIC_{90}s were 0.05 and 0.1 µg/ml, respectively), but not active against Listeria monocytogenes. Penicillin G was more active than ampicillin and piperacillin against group B streptococci (MIC_{90}s were 0.1, 0.12 and 0.24 µg/ml, respectively), and ampicillin was the most active against Listeria monocytogenes (MIC_{90} 0.6 µg/ml). Every double beta-lactam combination was synergic for 3-14% of Escherichia coli, 8-26% of group B streptococci and 67-100% of Listeria. The ceftriaxone combination was less synergistic than cefotaxime combinations. In time-kill evaluations using concentrations representative for cerebrospinal fluid, the killing kinetics of

Escherichia coli were not influenced by any combination. A significant delay in killing of group B streptococci was observed with penicillin G-cephalosporin and ampicillin-cephalosporin combinations. A significant increased killing of Listeria monocytogenes was observed with penicillin G-cephalosporin combinations. The other combinations did not alter the killing kinetics of group B streptococci and Listeria monocytogenes.

An outbreak of serious infections due to gentamicin-resistant Klebsiella pneumoniae occurred in a neonatal intensive care unit in which the combination of gentamicin sulfate and ampicillin sodium had been used for standard initial therapy for suspected sepsis for children nearly 11 years old (19). After institution of control measures that included the substitution of cefotaxime sodium for gentamicin in the standard regimen, the outbreak promptly subsided. Nevertheless, a second outbreak of serious infections due to cefotaxime-resistant Enterobacter cloacae began ten weeks later. Sequential stool cultures from patients in the unit confirmed the disappearance of gentamicin-resistant Klebsiella pneumoniae and the emergence of cefotaxime-resistant E cloacae after the change in antibiotic policy. These observations suggest that routine use of cephalosporins for therapy of suspected sepsis may lead to the emergence of drug-resistant microorganisms more rapidly than has occurred with the aminoglycosides.

Fifty children with bacterial meningitis were prospectively randomized to receive cefotaxime (50 mg/kg/dose every 6 hours), or ampicillin and chloramphenicol in standard doses (20). Twenty-three patients received cefotaxime and 27 patients received ampicillin and chloramphenicol. Bacterial isolates included: Haemophilus influenzae (n = 29), Streptococcus pneumoniae (n = 8), Neisseria meningitides (n = 8), group B streptococci (n = 3), and Salmonella enteritidis (n = 2). Then (34%) of the Haemophilus influenzae isolates were resistant to ampicillin, nine on the basis of beta-lactamase production. All strains were susceptible to cefotaxime (100%), and ampicillin-chloramphenicol (96%). The detectable sequelae were similar, at 78% and 77%, respectively. The duration of therapy, 11.1$\pm$2.4 days (range: 10 to 21 days), and 5.6$\pm$2.9 days (range: 2 to 17 days), respectively. No adverse drug reactions or side effects were noted in either group. Cefotaxime was found to be a safe and effective antibiotic for therapy of meningitis in children.

3-4. Treatment of bacterial meningitis with cefotaxime and other antibiotics in neonates and infants

Group B beta-hemolytic streptococci and Escherichia coli strains account for approximately two thirds of all cases of neonatal meningitis, while bacteria that typically account for meningitis in older groups (Haemophilus influenzae type B, Neisseria meningitis, and Streptococcus pneumoniae) are infrequent causes of meningitis in the neonatal population (21). Signs suggestive of meningeal irritation, including stiff neck, bulging fontanelle and convulsions were reported. Ampicillin and either gentamicin or cefotaxime are recommended for initial empiric therapy on neonatal meningitis. In general, penicillin G or ampicillin is preferred for group B streptococcal meningitis, ampicillin for Listeria monocytogenes meningitis, and ampicillin plus either an aminoglycoside or cefotaxime for gram-negative meningitis. For the very low-birth-weight neonates who have been in the nursery for a prolonged period of time, organisms such as enterococci and gentamicin-resistant gram-negative enteric bacilli must be considered. Empiric combinations of antibiotics for such patients would include ampicillin or

vancomycin, plus amikacin or cefotaxime. All neonates should undergo repeat cerebrospinal fluid examinations and culture at 48 to 72 hours after initiation of therapy. Therapy should be continued for 14 to 21 days for neonatal meningitis caused by group B streptococci or Listeria monocytogenes, and for at least 21 days for meningitis caused by gram-negative bacilli. All patients with neonatal meningitis should have hearing and development monitored serially. The first audiologic evaluation should occur 4 to 6 weeks after resolution of the meningitis.

Al-Harthi et al. (22) determined the prevalent agents for neonatal bacterial meningitis and their antibiotic susceptibility. Records of newborn infants with positive cerebrospinal fluid culture were retrospectively studied. A total of 1,473 entered the nursery, of which 32 episodes of meningitis occurred amongst 31 neonates. Klebsiella pneumoniae (31%), and Serratia marcescens (21%), were the main pathogens. The incidence of concurrent septicemia among these infants was 58%. Klebsiella pneumoniae appears to dominate in both early and late onset infections. Klebsiella pneumoniae and Serratia species were the leading agents for neonatal bacterial meningitis. The relatively high frequency of Serratia appears comparatively rare in other reports across the globe. Imipenem and cefotaxime, as the empirical antibiotics in infants with a clinical diagnosis of neonatal sepsis, are recommended.

Nwadioha et al. (23) determined the common etiologic of acute bacterial meningitis in children aged from 0 to 15 years and their antibiotic susceptibility in infants with suspected acute meningitis. A positive culture bacterial isolation rate of 3.3% (n = 50/1,500) with prevalence of Streptococcus pneumoniae (24%), Neisseria meningitis (22%), Escherichia coli (16%), Haemophilus influenzae (14%), and Group B streptococci (8%), were susceptible to ceftriaxone (96%), cefotaxime (95%), and ciprofloxacin (93%). The incidence of neonatal meningitis in England and Wales has not changed since a previous study in 1985-1987. However, the acute phase mortality has fallen from 19.8% in 1985-1987 to 6.6% in 1996-1997 (24). Group B streptococci (42%), and Escherichia coli (16%), remain the most common infecting microorganisms. Group B streptococci and Escherichia coli remain the most common infecting microorganisms. Eight of 69 (12%) neonates with group B streptococci, and 4/26 (15%) with Escherichia coli died. Antibiotic regimen based on the "third generation" cephalosporin, notably cefotaxime, were most commonly used (84%). Less than a third of samples from aseptic meningitis were examined for viruses; 56% of these were positive. Although the incidence of neonatal meningitis remains unchanged, mortality from these infections has fallen significantly. If this improvement is maintained as reflected in the level of sequelae at 5 years of age, the fear surrounding meningitis during the neonatal period will have been dramatically reduced.

A total of 85 neonates with bacterial meningitis had positive cerebrospinal fluid culture infections. The ages of these infants ranged from 1 to 28 days (25). The most common causative agents were group B beta-hemolytic streptococci (31.8%), followed by Escherichia coli (20%), Proteus mirabilis (7.1%), Enterobacter cloacae (5.9%), Chryseobacterium meningosepticum (5.9%), other streptococci excluding Streptococcus pneumoniae (4.7%), and Klebsiella pneumoniae (3.5%). Among 85 infants treated 51 (60%) were younger than 7 days. Among them, dyspnea was the most common clinical manifestation. Fever and diarrhea were more frequent in neonates with late onset of disease (after seven days

of age). Ampicillin and cefotaxime were the most commonly used antibiotics. The most frequently encountered complications were hydrocephalus and size. These were accompanied by a fall in the mortality rate, but a sustained high incidence of complications and sequelae were observed. The results of this study highlight the importance of developing strategies to prevent group B streptococcal infection.

Lecour et al. (26) treated 256 children suffering from bacterial meningitis with daily 150 to 200 mg/kg cefotaxime. The causative organisms were: Neisseria meningitides (n = 108), Streptococcus pneumoniae (n = 61), Haemophilus influenzae (n = 60), enteric gram-negative bacilli (n = 21), and Staphylococcus species (n = 6). A total of 240 patients (93.7%) were cured. Sterilization of cerebrospinal fluid was obtained in 214 (80%) children after the first 72 hours of treatment. Cefotaxime is an effective and safe drug for the treatment of childhood bacterial meningitis.

Seven neonates were treated with cefotaxime during eight episodes of gram-negative bacillary meningitis and sepsis (27). The causative organisms were Escherichia coli (n = 6), Klebsiella pneumoniae and Enterobacter sakazakii (n = 1, each). After identification of the pathogen, cefotaxime was used alone in six instances. Two infants with brain abscesses received adjunctive therapy with another antibiotic. Mean cerebrospinal fluid bactericidal titer was 1:64. The sterility of cerebrospinal fluid was documented after a mean of 3.3 days of therapy. All infants recovered with good neurologic outcome. Cefotaxime in a dosage of 150 mg/kg/day intravenously, divided every 6 hours, is a safe and effective therapy for neonatal gram-negative bacillary meningitis.

Riordan et al. (28) treated 44 infants aged less than 3 months and suffering from bacterial meningitis, and determined the causative organisms and the antibiotic sensitivity. Forty infants had either febrile, irritability or seizures on the day of admission. Group B Streptococcus and Neisseria meningitides were the commonest causes of meningitis. All organisms, except one, were sensitive to ampicillin and/or cefotaxime. Initial treatment with ampicillin and cefotaxime is appropriate.

Kaplan and Patrick (29) reviewed cases of gram-negative enteric bacillary meningitis in infants and children treated with cefotaxime. Seventeen of 20 children were 2 days to 12 years old (median 12 days). The etiologic organisms in these 20 children were Klebsiella species (n = 9); Escherichia coli (n = 4); Enterobacter cloacae (n = 3); Citrobacter diversus (n = 2); other (n = 2). With the exception of one isolate of Acinetobacter, all isolates were susceptible to cefotaxime. In addition to cefotaxime, 17 children received an aminoglycoside intravenously. Children with meningitis caused by Klebsiella species or non-Klebsiella organisms received cefotaxime for 31 ± 14 and 37 ± 17 days, respectively. Aminoglycosides were administered for 16 ± 10 days. The mean duration of positive lumbar, cerebrospinal fluid or brain abscess cultures were 5.8 ± 4.7, and 7.2 ± 5.0 days after the start of therapy in the Klebsiella and non-Klebsiella meningitis patients, respectively. Gram-negative enteric meningitis remains difficult to treat despite the excellent in vitro activity of cefotaxime against gram-negative enterics, in part as a result of the predisposing conditions resulting in the development of this infection.

Eighteen low-birth-weight newborns with a body weight ranging 500 to 1,500 grams and a mean gestational age of 28.4 ± 2.4 weeks, during the first week of life were enrolled in the study (30). The neonates received a single 50 mg/kg daily dose of cefotaxime. In a non-comparative

prospective clinical trial, 22 infants (one week to three months old) were treated with a dose of cefotaxime of 50 mg/kg/day. The predominant pathogen was Escherichia coli (n = 14), and Enterobacter cloacae (n = 4). Cultures of the cerebrospinal fluid obtained 24-48 hours after the initiation of treatment were sterile in all subjects. Survival and complication rates of 95% and 19%, respectively, were observed. Cefotaxime is excellent with no adverse effects.

Eighteen infants and children (1 week to 3 months of age) were treated with cefotaxime 200 mg/kg/day for gram-negative enteric bacillary meningitis (31). Seventeen of these patients (94.4%) survived, with a complication rate of 23.5% (4/17 patients). The follow-up cerebrospinal fluid cultures at 24 hours from the initiation of the therapy were sterile in all patients. Cefotaxime is a safe and effective agent in the treating of gram-negative enteric bacillary meningitis in infants and children and should be considered as a potential drug of choice in gram-negative neonatal meningitis due to susceptible organisms.

Purulent meningitis is a life-threatening disease in tropical areas. This disease results from underlying malnutrition, hemoglobinopathy and enzymopathy, but also from delays in treatment. Sow (32) have treated 28 patients, aged from 16 days to 7 years, suffering from purulent meningitis, with daily doses of 90 to 200 mg/kg cefotaxime (mean 150 mg/kg). Almost half of the patients were suffering from malnutrition and low body weight, or from hemoglobinopathy. Cefotaxime showed a care of 79% patients and a complete recovery in 71% of children.

3-5. Comparison of the efficacy of cefotaxime with other antibiotics in the treatment of neonatal bacterial meningitis and sepsis

A single-blind trial, using randomly either cefotaxime or a benzyl-penicillin-gentamicin, was carried out on 68 hospitalized pediatric patients with 72 episodes of severe septicemia and neonatal meningitis (33). One group of patients received cefotaxime and another group received penicillin and gentamicin. A cure rate of 94.4% was obtained with cefotaxime compared with 72.2% in the other group. One patient with bacterial meningitis treated initially with cefotaxime died a month later, and five deaths were observed after the treatment with penicillin and gentamicin. These results indicate that cefotaxime should be considered a drug of choice in many neonates with life-threatening sepsis and meningitis.

Thirteen children with meningitis due to Haemophilus influenzae, group B beta-hemolytic streptococcus, Streptococcus pneumoniae, Staphylococcus epidermidis, Neisseria meningitides, Escherichia coli, or Pseudomonas aeruginosa were unsuccessfully treated with different antibiotics. These children were treated with intravenous cefotaxime and nine children were cured. One case of infection (with a different organism) was successfully treated with cefotaxime (34). One child died from his underlying disease (astrocytoma); one child was cured with sequelae (hydrocephalus). A further child with meningitis caused by Escherichia coli had been treated unsuccessfully by intravenous and intraventricular chloramphenicol and gentamicin. Intravenous and intraventricular cefotaxime administrations cured this child. Cefotaxime treatment was well tolerated.

The clinical and microbiological data of 60 neonates with meningitis were assessed by Adhikari et al. (35). Twenty-three neonates were enrolled by the Neonatal Unit (Group 1), and 37 by the General Pediatric Wards (Group 2). The overall prevalence/1000 was significantly lower in Group 1 (0.36)

than in Group 2 (1.11; $p < 0.0001$). Streptococcus agalactiae isolates (n = 21; 35%), Klebsiella pneumoniae (n = 17; 28%), and Escherichia coli (n = 10; 17%), were the commonest pathogens accounting for 80% of the cases. Amikacin was administered to all neonates. Streptococcus agalactiae isolates were susceptible to penicillin and chloramphenicol. Gram-negative isolates showed resistance to ampicillin, chloramphenicol and sulphamethoxazole-trimethoprin.

Klebsiella pneumoniae isolates were resistant to gentamicin and amikacin. All isolates were fully susceptible to cefotaxime. Sixty-two bacteriologically confirmed cases of bacterial meningitis were obtained retrospectively from infectious disease consultants (36). One of the two most common organisms was the pneumococci, the other organism was Klebsiella. The treatment with cefotaxime resulted in the cure and survival rates of 85%. Failure of monotherapy was seen in one case of Pseudomonas meningitis, as well as in three of five cases of Enterobacter meningitis. Two cases of Escherichia coli meningitis, in which moxalactam therapy inexplicably failed, were cured with cefotaxime. Close analysis of killing kinetics appeared to explain the Enterobacter and Escherichia coli failures. Not all gram-negative species isolates that cause meningitis can be successfully treated by cephalosporins.

3-6. Bacterial susceptibility to cefotaxime and other antibiotics in neonates and infants

Among 831 cases of neonatal bacterial meningitis occurring from 2001 to 2013, Neisseria meningitides was the third most frequent bacterial sepsis found (37). All cases occurred only in term neonates and were mainly late onset. Serogroup B accounted for 78% of cases. At diagnosis, 27% of cases had at least one sign of disease severity. All strains were susceptible to cefotaxime, but 12% showed intermediate susceptibility to penicillin G and to aminopenicillin. Of 280 samples tested, 52 (18.6%), were positive to Cronobacter species (38). Sequence typing and antimicrobial sensitivity determination/gram was 78.8% (41/52) of samples. The results of the O-antigen serotyping for 111 isolates showed that Cronobacter sakazakii serotype O2 (28 isolates) was the most prevalent serotype. Multilocus sequence typing analyses produced 41 sequence types, including 20 novel sequence types. Sequence type 8 was the most prevalent ST (9 isolates) followed by sequence type 4 (5 isolates). Antimicrobial sensitivity testing showed that 84.5%, and 46.5% of the isolates were resistant to penicillin G and cephalotin, respectively; in contrast, all the isolates were susceptible to cefotaxime, ciprofloxacin, tetracycline, and nalidixic acid.

Out of 120 neonates suspected of having neonatal sepsis, 30.8% (37/120) were blood culture positive (39). The most common causative agents of neonatal sepsis was Staphylococcus aureus (56.8%; 21/37) followed by Klebsiella pneumoniae (21%; 8/37), Pseudomonas aeruginosa (13.4%; 5/37) and others. Neonatal sepsis was more frequent in male neonates (32.5%) than in female neonates (26.5%) the ratio was 1.2:1 ($p > 0.05$). Neonatal sepsis was significantly higher (58.3%) in low-birth-weight neonates (< 2.5 kg body weight) compared with appropriate-birth-weight (23.9%) ($p < 0.05$). Prevalence was higher in preterm neonates (57.8%; 11/19) as compared with term neonates (25.7%; $p= 0.05$). Generally, all of isolates were sensitive to most of the antibiotics used as first line drugs like amikacin, gentamicin, cefotaxime and ampicillin except Acinetobacter baumanii. This organism was only sensitive towards cotrimoxazole, azithromycin, cefotaxime and ceftazidime.

Out of 331 blood specimens cultured, the prevalence of confirmed bacterial sepsis

was 25.9% (86/331) (40). Point prevalence for confirmed cases was 44.4% (28/63) from neonatal intensive care units and 21.6% (58/266) from the pediatric ward. Gram-positive cocci were the predominant isolates with Coagulase positive (32.2%), and Coagulase-negative (28.7%). Staphylococci accounted for 60.9% of the total isolates. Gram-negative rods comprised 39.1% of all isolates with Klebsiella, Escherichia coli and Salmonella being the most common organisms isolated. Klebsiella was the most frequent gram-negative road from the neonatal intensive care unit and Salmonella typhi was predominantly isolated road from the pediatric ward. Acinetobacter showed 100.0% susceptibility to ceftriaxone and cefotaxime, but was resistant (100.0%) to ampicillin, tetracycline and cotrimoxazole. Escherichia coli and Klebsiella were 80.0% and 91.0% susceptible to ceftriaxone and cefotaxime, respectively. Klebsiella species showed 8.3% susceptibility to tetracycline, but was resistant to ampicillin and cotrimoxazole. Escherichia coli showed 40.0% susceptibility to ampicillin, chloramphenicol and cotrimoxazole, and 20.0% susceptible to tetracycline, and 80.0% susceptible to gentamicin, and cefuroxime. Coagulase negative Staphylococci was susceptible to gentamicin (72.0%), but Coagulase positive Staphylococci showed intermediate sensitivity to gentamicin (42.9%).

Specimens (n = 217) yielded 131 Salmonella typhi (30.36%), 71 Salmonella paratyphi-A (32.71%), and Salmonella paratyphi-B (6.9%). These were sensitive to quinolones (n = 91; 94.96%), ciprofloxacin (n = 182; 96.4%), ofloxacin (n = 203; 95.74%), and cephalosporins (n = 202; 96.62%), cefotaxime (n = 206; 99.17%, and ceftriaxone (n = 208; 98.79%) (41). Resistance to amoxicillin was (n = 128; 96.48%), and to cotrimoxazole (n = 78; 29.91%). A total of 136 (62.64%) of the isolates were multidrug resistant. Ciprofloxacin is a suitable empirical choice in presumed enteric fever cases, but culture and sensitivity analysis should be performed in prescription strategy. Group B Streptococcus is one of the leading causes of neonatal bacterial infections. The incidence of the Group B Streptococcus-related invasive diseases is 0.13 per 1,000 live births (42). Analysis of Group B Streptococcus samples obtained from 60 invasive cases showed that the most frequent serotypes were III (48.3%), Ia (30.0%), and Ib (10%). All isolates were susceptible to penicillin G, ampicillin, cefotaxime, and panipenem.

Bhat et al. (43) studied the frequency of bacteria isolates in early onset neonatal sepsis and their sensitivity pattern. Of 2,182 neonates screened, 389 (17.8%) had positive blood cultures. Preterm neonates were 40.6% and small for gestational age were 18.3%. Mean birth weight was 2,344 grams. Gram-negative species represented 90.8% of culture isolates. Pseudomonas (33.2%), and Klebsiella (31.4%) were the common isolates. The pathogens included were Acinetobacter (14.4%), Staphylococcus aureus (9.2%), Escherichia coli (4.4%), Enterobacter (2.2%), Citrobacter (3.1%), and Enterococci (2.2%). In the gram-negative group, best susceptibility was Amikacin (74.5%), followed by other aminoglycosides, and by ciprofloxacin and cefotaxime. The susceptibility was remarkably low to ampicillin (8.4%). The gram-positive group had susceptibility of 42.9% to erythromycin, 47.6% to ciprofloxacin and above 50% to aminoglycosides. Of all isolates, 83.8% were susceptible to either cefotaxime or amikacin. Gram-negative species, especially Pseudomonas and Klebsiella, were the predominant causative organisms. An initial empirical choice of

cefotaxime in combination with amikacin appeared to be rational choice for a given cohort. A total of 1,050 neonates were admitted to the hospital, and 174 (16.5%) neonates had positive blood culture (44). Of the 527 neonates with risk factors and clinical features of sepsis, 174 (33.3%) had confirmed sepsis, 119 (22%) had early-onset sepsis, while 55 (10.4%) had late-onset sepsis. The incidence of neonatal sepsis in the hospital was 51.3/1,000 live births. Weight less than 1,500 grams, prolonged rupture of membranes and lower socio-economic status were risk factor for sepsis. Staphylococcus (31.0%), Klebsiella (23.0%), coagulase-negative Staphylococcus (12.6%), and Escherichia coli (11.0%) were the leading etiologies. The isolates were most sensitive to levofloxacin (95.7%), ofloxacin (95.1%), cefotaxime (86.7%), and ceftazidime (81.3%).

Ruess et al. (45) investigated the susceptibility patterns of 190 group B streptococci strains from neonates and 150 group B streptococci strains collected from adult women. All isolates were susceptible to penicillin, ampicillin and cefotaxime. Erythromycin resistance among all isolates from neonates and from adult women was 4.7% and 6%, respectively. In contrast, 12% of the isolates from adult women were resistant to erythromycin and 7% were resistant to clindamycin. These findings show an increasing macrolide resistance in group B streptococci strains and indicate the need for further surveillance.

Oundo et al. (46) determined the antibiotic susceptibility patters and genotypes of non-typhi Salmonella isolates from children. Overall positive cultures were obtained in 543 (14%) of 3,885 blood samples, 364 (30%) of 1,210 stool samples and 143 (11%) of 1,283 cerebrospinal fluid samples. Non-typhi Salmonella samples were isolated in 151 (27.8%), 72 (19.8%), and 11 (7.7%) of these positive cultures, respectively. The total of 234 non-typhi Salmonella isolates were serotyped; the most frequent were Salmonella enteric serotype Enteritidis (41%), and Salmonella enterica serotype typhimurium (38%). Antibiotic sensitivity testing was done using ampicillin, chloramphenicol, gentamicin, cotrimoxazole, cefuroxime, cefotaxime, amoxicillin-clavulanic acid, and tobramycin. Of 234 isolates, 43 were sensitive to all antibiotics tested and 133 were multi-drug resistant. The present results indicate a high proportion of multi-drug resistant among the isolates from Kilifi (coast of Kenya). Oundo et al. (46) conclude that 2 major serotypes of salmonella, i.e., Salmonella enterica serotype Typhimurium and Salmonella enterica serotype Enteritidis, of micro-epidemic nature that have been previously unrecognized in Kilifi are responsible for infection in Kilifi district on the coast of Kenya and that over half (56.8%) of the total of non-typhi Salmonella isolates are multidrug resistant.

The serotypes and levels of antibiotic resistance of 59 Streptococcus agalactiae isolates from neonates in Casablanca were studied by Aitmhand et al. (47). Most of the isolates (86.4%) were recovered from early-onset disease. The serotype distribution was as follows: serotype III 39%; serotype Ia 32.2%; and serotype V 10.2%. All strains were susceptible to penicillin G, cefotaxime and ampicillin, whereas 1 strain was resistant to erythromycin. No high level of resistance to gentamicin was detected. The antibiotic susceptibility patterns reported by these authors support the recommended treatment and prophylaxis of invasive group B streptococcal disease.

Blood and cerebrospinal fluid isolates (n = 629) from Swedish infants up to one year of age were tested in vitro against 13 antimicrobial agents in order to update the guidelines for empiric therapy of septicemia and meningitis (14). Ampicillin

plus gentamicin provided inadequate empiric therapy for meningitis, due to the poor cerebrospinal fluid penetration of the aminoglycoside and the frequent occurrence of bacterial resistance to ampicillin. Ceftazidime and cefuroxime were moderately active. Cefotaxime is the best empiric therapy for septicemia and meningitis in infants. Because of the occurrence of Listeria and enterococcal infections, ampicillin should initially be added and other combinations are also advisable for the occasional cases of Enterobacter, Citrobacter, Serratia, and Pseudomonas infections. For coagulase-negative staphylococci only vancomycin offered a broad activity (100% at achievable serum levels).

Neonatal meningitis is caused by group B streptococci, Escherichia coli, and Listeria monocytogenes, in order of frequency. Bradsher and Ulmer (48) found that clinical isolates of group B streptococci and Listeria monocytogenes did not demonstrate uniform susceptibility to beta-lactam antibiotics. Antibiotic potencies for group B streptococci tested were cefotaxime, penicillin, ceftriaxone, amoxicillin, cefamandole, cephalotin, and moxalactam. N-Formimidoyl thienamycin (MK0787) was the 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 organism has been characterized with antibiotic susceptibility.

The susceptibility of 100 groups of B streptococci to 16 beta-lactam antibiotics was tested by agar dilution (49). Penicillin G and N-Formimidoyl thienamycin were the most active agents tested, both having a MIC_{90} of 0.06 µg/ml. Ceftriaxone, cefotaxime, cefamandole, and cefotaxime were active, all having a MIC_{90} of 0.12 µg/ml, and ampicillin, cephalotin, and mezlocillin all had a MIC_{90} of 0.25 µg/ml. The MIC_{90} for piperacillin, cefoperazone, and ceftazidime was 0.5 µg/ml; least active were Carbenicillin, ticarcillin, cefoxitin, and moxalactam and their MIC_{90}s were 1, 2, 4, and 8 µg/ml, respectively. No penicillin-tolerant strains were detected.

One hundred and twenty-six clinical isolates of Escherichia coli from cerebrospinal fluid of neonates were tested for sensitivity to five antibiotics (50). The most useful of the generally recommended initial therapies, is a combination of ampicillin and gentamicin, and is supported in the majority of cases. On the basis of the in vitro results, cefotaxime would have been effective as a therapy for all cases. Ampicillin and cefuroxime resistance occurred mostly in neonates who had received antibiotics prophylactically and neonates whose mothers had fever during labour or in neonates who had been nursed in incubators for more than one week.

3-7. Bacterial resistance to cefotaxime and other antibiotics

Neonatal sepsis remains a serious problem in any neonatal intensive care unit. Bacterial organisms have developed increased resistance to commonly used antibiotics (51). Almost one-third of the admitted neonates (33.4%) were diagnosed as having neonatal sepsis, 32.25% of them were culture-proven. Early and late onset sepsis was found in 35.4% and 25.6%, respectively. Fungal infection was detected in 9% of isolates. Escherichia coli were the main pathogen isolated in both early and onset sepsis (24.5%). Overall, 77% of the isolates were multidrug-resistant (60% of gram-positive bacteria and 83.4% of gram-negative bacteria). A 79% of mortality was caused by multidrug-resistant organisms. Gram-positive and gram-negative bacteria showed high resistance against commonly used antibiotics such as ampicillin, cefotaxime, ceftriaxone, and gentamicin.

There is an alarming increase in antibiotic resistance to the commonly used antibiotics. Acinetobacter baumanii is an important hospital-acquired pathogen in intensive care unit. Healthcare facilities and ventilator-associated pneumoniae frequently cause bacteremia. It is difficult to treat Acinetobacter baumanii infections because of their highly resistant antimicrobial profiles (52). All the Acinetobacter baumanii isolates showed 100% resistant to ampicillin, amoxicillin, cefuroxime, cefuroximine axetil, cefoxitin, cefotaxime, and nitrofurantoin. Seven percent of Acinetobacter baumanii isolates were resistant to amikacin. Two percent of the Acinetobacter baumanii isolates were classified as having intermediate susceptibility to tigecycline. Acinetobacter baumanii isolates showed an antibiotic resistance profile of 67% and higher to antibiotics, such as ceftazidime, cefepime, imipenem, gentamicin, ciprofloxacin, and trimethoprim/sulfamethoxazole. None of the isolates were resistant to colistin. The high prevalence of multidrug-resistant Acinetobacter baumanii isolates has a severe impact on available treatment choices and this in return impacts on treatment outcomes in the studied healthcare facilities.

Viswanathan et al. (53) reported results on the incidence and etiology of neonatal sepsis cases admitted to a facility in a rural area in eastern India. Blood culture was done for all neonates, with suspected clinical sepsis. In total, 216 neonatal blood culture samples were processed, of which 100 (46.3%) grew potential pathogens. Gram-negative infection was predominant (58/100 cases) mainly caused by enteric gram-negative bacteria. Klebsiella pneumoniae was the most common gram-negative isolate. The emergence of fungal infection was observed, with 40% of the infection caused by yeast. Gram-negative organisms exhibited 100% resistance to ampicillin, cefotaxime, and ciprofloxacin. Carbapenem showed emerging resistance (n =4; 6.6%). Results of analysis of risk factors showed an extremely significant association between gestation and sepsis, and gender and sepsis. Gastrointestinal symptoms were highly specific for fungal infections. One-third of neonates (n = 29), who developed culture-positive sepsis died. Blood culture is an investigation which is frequently unavailable in rural India. As a result, empirical antibiotic therapy is commonly used. These findings attempted to provide data for evidence-based antibiotic therapy given to sick newborns in such rural units. The present results suggest that there is a high rate of antibiotic resistance in rural India.

Hammoud et al. (54) investigated the incidence, etiological pattern and the antimicrobial resistance of late-onset neonatal infections over a period of 5 years. The overall incidence was 16.9 (95% confidence interval: 15.8-18.0) episodes per 1,000 live births. The commonest pathogen was coagulase Staphylococcus, 339 (35.7%), while Klebsiella was the most common gram-negative infection, 178 (18.8%). Escherichia coli, Enterococcus and Enterobacter species were each responsible for 6% of all infections. Candida caused 104 (11.0%) infections. The general pattern of infections remained unchanged over the study period. Case fatality was 11.7% (95% confidence interval: 9.7%-13.9%), and was high for Pseudomonas (18.4%), and Candida (22.1%) infections. Approximately 24% and 20% of Klebsiella infections were resistant to cefotaxime and gentamicin, respectively, while 28% and 24% of Escherichia coli infections were resistant to cefotaxime and gentamicin, respectively. The incidence of late-onset infection in Kuwait is high, resembling that in resource-poor countries. Prevention against nosocomial infections in neonatal units has the potential to further reduce neonatal mortality in these settings. A

preterm infant with early onset Morganella morganii sepsis was treated with cefotaxime and gentamicin after confirmation of antimicrobial susceptibility (55). The infant developed persistent ventriculitis caused by the emergence of a cefotaxime-resistant Morganella variant with depression of its AmpC β-lactamase. When choosing antibiotic therapy, the risk of development of resistance to cephalosporins should be considered in infection caused by Morganella morganii and other gram-negative organisms with inducible AmpC β-lactamases.

Occurrence and transferability of beta-lactam resistance in 30 multi-resistant Escherichia coli, Klebsiella species, Enterobacter species, Pantoea agglomerans, Citrobacter freundii and Serratia marcescens strains isolated from children between 0 and 3 years of age were assessed by Bujdakova et al. (56). The strains were resistant to ampicillin (n = 30), cefoxitin (n = 22), cefotaxime (n = 30), ceftriaxone (n = 30), ceftazidime (n = 30), and aztreonam (n = 28), but susceptible to cefepime (n =30), and imipenem (n = 26). Twenty-eight of 30 isolates possessed a transferable resistance confirmed by conjugation and isolation of 79-89-kb plasmids. The beta-lactam resistance was due to production of beta-lactamase and ceftazidime proved to be stronger β-lactamase inductor than ceftriaxone. Twenty-five clinical isolates expressed transferable extended spectrum β-lactamases, and chromosomally encoded AmpC β-lactamase.

In a 12-month period, 561 stool culture samples were assed from Yemeni children aged 1 to 60 months. The patients presented diarrhea, and were analyzed to identify the bacterial etiology and their anti-microbial resistance to the commonly used antibiotics (57). A total of 190 (33.9%) samples were positive for bacterial culture. Most of the positive cultures (58%) were from children 1 to 12 months old. The majority of the positive cultures were Escherichia coli (58.4%), Salmonella species, and Shigella species (20% each). Campylobacter was found to be an extremely uncommon agent of childhood diarrhea making up only 1.6% of the positive cultures. The majority of the Salmonella were group C (60.5%) and group B (29%). Of Shigella isolates, 13 (34%) were Salmonella Flexner, and 7 (18%) Salmonella dysentery. More than two-thirds of the Salmonella isolates were resistant to nalidixic acid, chloramphenicol, cotrimoxazole, gentamicin, and ampicillin, while 42% were resistant to cefotaxime. Most of Shigella isolates were susceptible to nalidixic acid and cefotaxime, and resistant to the other antibiotics. All tested Escherichia coli isolates were resistant to amoxicillin (83%) and to cotrimoxazole (62%) to chloramphenicol and gentamicin (54% each), while only 16% and 6% were resistant to nalidixic acid and cefotaxime, respectively. This study draws attention to the urgent need of a surveillance system, essential for the containment of anti-microbial resistance.

Fiore et al. (58) analyzed data from 109 cases of pneumococcal meningitis. Pneumococcal isolates were resistant to cefotaxime (9%), and 11% of the pneumococcal isolates had intermediate susceptibility to cefotaxime. Children were likely to have cephalosporin-nonsusceptible pneumococcal meningitis, but mortality was significantly higher among adults aged 18-64 years. Vancomycin was given upon admission to 29% of patients, and within 48 hours of admission to 52% of patients. Nonsusceptible cefotaxime was associated with the following outcomes: increased mortality, prolonged length of hospital or intensive care unit stay, requirement of intubation or oxygen, intensive care unit care, discharged to another medical or

long-term-care facility, or neurologic deficit. Empirical use of vancomycin, current prevalence of drug-resistant Streptococcus pneumoniae, and degree of no-susceptibility to cefotaxime may have influenced these findings.

3-8. Pharmacokinetics of cefotaxime in neonates and infants

Cefotaxime, a bactericidal "third-generation" cephalosporin, is the antibiotic of choice for the management of neonatal bacterial meningitis and sepsis. Because of the maturation of hepatic and renal functions in the first month of life, pharmacokinetic parameters of drugs are continuously changing, dependent not only on postnatal age, but also on gestational age (59). In neonates, the half-life of cefotaxime ranges from 2 to 6 hours and varies with the gestational and postnatal ages (1). This antibiotic must be administered intravenously or intramuscularly because it is not absorbed by the gastro-intestinal apparatus. The short half-life of cefotaxime requires that this antibiotics be administered at 6 hour intervals. Aujard et al. (59) measured the concentrations of cefotaxime in 30 hospitalized neonates with a gestational age ranging from 28 to ≥ 37 weeks (**Table.1**), and studied the pharmacokinetics of cefotaxime in these neonates (**Table.2**).

Cefotaxime was infused intravenously over a period of 20 min. Blood samples of 200 µl were obtained using the heel prick technique at 5, 15, 30 min, and 1, 4, and 8 hours after the administration. The lowest trough concentrations of cefotaxime were observed in term neonates and were more than 10 times the MIC_{90} of Escherichia coli (0.20 µg/ml), and more than 30 times the MIC_{90} of group B streptococcus (0.06 µg/ml). The half-life, the clearance, and the distribution volume of cefotaxime were 3.49±0.45 hours, 1.08±0.04 l/kg/h, and 0.34±0.04 l/kg, respectively, in neonates with a gestational age < 32 weeks, and were 2.77±0.49 hours, 2.25±0.47 l/kg/h, and 0.36±0.08 l/kg, respectively, in neonates with a gestational age ≥ 37 weeks (59). The cefotaxime half-life and the clearance correlated with the gestational and postnatal ages. In preterm infants the elimination half-life of cefotaxime was longer than in term infants (**Table.3**).

Kafetzis et al. (60) studied the pharmacokinetics and efficacy of cefotaxime in 36 neonates with severe gram-negative bacterial infections. Eighteen neonates were preterm; 10 were less than one week old, and 8 were 1 to 4 weeks old. The half-life and the clearance of cefotaxime were 5.7±0.8 hours and 1.37±0.15 ml/min, respectively, in preterm neonates with a postnatal age < 1 week, and 2.0±0.4 hours and 4.45±0.61 ml/min, respectively, in term neonates with a postnatal age of 1 to 4 weeks (**Table.3**). **Table.4** shows the concentrations of cefotaxime in the cerebrospinal fluid and serum. Cefotaxime was administered intravenously over one to two min. Individual doses of cefotaxime were 25 mg/kg and 50 mg/kg in neonates with bacterial meningitis. The cerebrospinal fluid concentration of cefotaxime ranged from 12.1 to 30.0 µg/ml and the serum concentration of this antibiotic ranged from 25.8 to 52.0 µg/ml. The cerebrospinal fluid to serum concentration ratios of cefotaxime ranged from 0.27 to 0.58 (60), and individual values are summarized in **Table.4**. Single-dose pharmacokinetics of 50 mg/kg administered intravenously were evaluated in 18 very-low-birth-weight neonates during the first week of life. The gestational age and the body weight of these neonates were 28.4±2.4 weeks and 1,015.6±349.8 grams, respectively. The postnatal age was 4.0±1.6 days (61). The half-life, the clearance, and the distribution volume ranged from 3.4 to 6.4 hours, from 0.05 to 0.10 l/h/kg, and from 0.31 to 0.79 l/kg, respectively (**Table.5**). A two-compartment open model best

characterized the disposition of cefotaxime during a 24-hour post-dose period. Jacobs and Kearns (30) reported the MIC_{50} and the MBC_{50} values for different bacteria, and they are summarized in table 6. The MIC_{50} (µg/ml) ranged from 0.006±0.005 to 0.062±0.034 and the MBC_{50} (µg/ml) ranged from 0.040±0.027 to 0.240±0.027.

Table-1: Serum cefotaxime concentrations (µg/ml) in neonates. Cefotaxime was infused intravenously at the dose of 25 mg/kg to 30 neonates. The figures are the mean±SD, by Aujard et al. (59).

Gestational age (weeks)						
	< 32		32-36		≥ 37	
	n = 3	n = 4	n = 7	n = 5	n = 6	n = 5
Postnatal age (days)	< 7	≥ 7	< 7	≥ 7	< 7	≥ 7
Time						
5 minutes	73.8±9.6	91±14.3	67.5±6.7	73.3±4.7	59.2±5.6	68.2±9.6
15 minutes	67.8±5.3	76±5.6	61.3±4.2	68.4±3.8	49.4±4.1	73±13.4
30 minutes	68.8±4.1	55.4±12.2	55.1±3.9	61.9±3.0	46.9±4.5	52.6±8.3
4 hours	31.3±0.73	37.5±8.9	25.7±1.4	20.7±3.5	16.9±3.4	16.8±2.1
8-11 hours	11.1	8.3±2.4	7.4±0.6	3.4±1.3	4.9±1.4	2.2±1.3

n = number of cases.

Table-2: Pharmacokinetic parameters of cefotaxime in neonates. Cefotaxime was infused intravenously at the dose of 25 mg/kg to 30 neonates. The figures are the mean±SD, by Aujard et al. (59).

Gestational age (weeks)						
	< 32		32-36		≥ 37	
	< 7 PNA (days)	≥ 7 PNA (days)	< 7 PNA (days)	≥ 7 PNA (days)	<7 PNA (days)	≥ 7 PNA (days)
Half-life (hours)	3.49±0.45	3.72±0.85	3.28±0.35	2.0±0.24	2.77±0.49	2.01±0.57
Clearance (l/kg/h)	1.08±0.04	1.17±0.29	1.45±0.05	1.87±0.18	2.25±0.47	2.33±0.46
Distribution volume (l/kg)	0.34±0.04	0.32±0.03	0.40±0.03	0.31±0.02	0.45±0.04	0.36±0.08
AUC (mg/l/h)	262.5±45.8	338.3±46.9	248±10.0	223.7±23.3	198.2±29.5	177.7±25.4

PNA: postnatal age.

Table-3: Pharmacokinetic parameters of cefotaxime in neonates. Cefotaxime was administered intravenously at dose of 25 or 50 mg/kg to 36 neonates with bacterial meningitis. The figures are the mean±SEM, by Kafetzis et al. (60).

Variables	Preterm neonates		Term neonates	
	< 1 week	1-4 weeks	1 week	1-4 weeks
Distribution half-life (min)	22±6	15±3	16±4	7±2
Elimination half-life (hours)	5.7±0.8	3.0±0.5	3.4±0.3	2.0±0.4
Distribution volume (l)	0.61±0.05	0.53±0.07	0.68±0.08	0.69±0.08
Clearance (ml/min)	1.37±0.15	1.79±0.08	2.30±0.19	4.45±0.61

Table-4: Cefotaxime concentrations in serum and cerebrospinal fluid after an intravenous dose of 50 mg/kg to 5 neonates with bacterial meningitis, by Kafetzis et al. (60)

Patients	Hours after administration	Cefotaxime concentration (µg/ml)		Ratio cerebrospinal fluid/serum
		Cerebrospinal fluid	Serum	
1	2	27.2	42.8	0.63
1	2	13.2	31.6	0.42
1	2	12.1	38.4	0.31
2	1	30.0	52.0	0.58
2	1	20.0	45.0	0.44
3	1	14.0	34.0	0.41
4	1	21.0	48.2	0.43
4	1	19.6	34.6	0.56
5	1	7.1	25.8	0.27

Table-5: Pharmacokinetic parameters of cefotaxime in 18 very-low-birth weight neonates after intravenous infusion of 50 mg/kg cefotaxime. The figures are the mean±SD for Tmax and Cmax, in other parameters the figures are the mean±SEM. The range of all parameters is reported in parenthesis, by Kearns et al. (61).

Tmax	Cmax	α	β	Half-life	Clearance	Distribution volume
(hours)	(mg/l)	($hours^{-1}$)	($hours^{-1}$)	(hours)	l/h/kg)	(l/kg)
0.083	159.02±11.59	7.41±1.7	0.156±0.008	4.44	0.074±0.03	0.461±0.027
	(95.48-273.20)	(0.3-32.9)	(0.11-0.20)	(3.4-6.4)	(0.05-0.10)	(0.31-0.79)

Table-6: MIC_{50} and MBC_{50} values of cefotaxime for different bacteria. The figures are the mean±standard deviation, by Jacobs and Kearns (30)

Organisms	Number of cases	MIC_{50} (µg/ml)	MBC_{50} (µg/ml)
Haemophilus influenzae	29	0.024±0.026	0.064±0.054
β-Lactamase (+)	9	0.041±0.036	0.084±0.071
B-lactamase (-)	20	0.006±0.005	0.040±0.027
Streptococcus pneumoniae	8	0.062+0.034	0.240±0.027
Neisseria meningitis	8	0.057±0.088	0.283±0.44

4-DISCUSSION

Cefotaxime is the antibiotic of choice for the management of the neonatal meningitis and sepsis. Cefotaxime is a bactericidal "third generation", cephalosporin and has a broad-spectrum against gram-positive microorganisms; also has an exceptional activity against gram-negative microorganisms (1). Cefotaxime is active against Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella specimens, Staphylococcus, Enterobacter specimens, and Haemophilus parainfluenzae, Pseudomonas aeruginosa, Escherichia coli, Citrobacter freundii, and Klebsiella pneumoniae (5).

Like other cephalosporins, cefotaxime kills bacteria by interfering with the synthesis of their cell walls (2). The diffusion in tissues and the penetration into the cerebrospinal fluid of cefotaxime are good. In neonates, the half-life of cefotaxime range from 2 to 6 hours and varies with the gestational and postnatal ages. Because of the short half-life of cefotaxime this antibiotic must be administered every 6 hours (1). Cefotaxime is not absorbed by the gastro-intestinal apparatus and thus must be administered intravenously or intramuscularly. In neonates, the mean trough serum concentration of cefotaxime and the cerebrospinal fluid concentration 1 hour after the intravenous administration of 50 mg/kg are 3.66±5.65 µg/ml, and 3.72±5.57 µg/ml, respectively (4). The MIC_{50} (µg/ml) and the MBC_{50} (µg/ml) of cefotaxime are 0.024±0.026, and 0.064±0.054, respectively, for Haemophilus influenzae, 0.062±0.034, and 0.240±0.027, respectively, for Streptococcus pneumoniae, and 0.057±0.088, and 0.284±0.44, respectively, for Neisseria meningitis (30). Therefore, the serum trough concentration and the cerebrospinal fluid concentration of cefotaxime, after an intravenous dose of 50 mg/kg, are remarkably higher than the MIC_{50} and MBC_{50} for Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitis.

Lecour et al. (3) treated children affected by bacterial meningitis with intravenous daily doses of 150 to 300 mg/kg of cefotaxime. The concentration of cefotaxime in the cerebrospinal fluid range from 0.499 to 2,829 µg/ml and the sterilization of cerebrospinal fluid was achieved in the first 72 hours of treatment in 90.1% of children. The causative organisms were Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, enteric gram-negative bacilli, and Staphylococcus species. A percentage of 92 of children were cured. Group B streptococcus is the most common etiologic agent, while Escherichia coli is the most common cause of mortality (11). Seventy-two infants suffering from gram-negative bacteria received cefotaxime or

ceftazidime. The Predominant infecting microorganisms were Escherichia coli infections and were sensitive to both cefotaxime and amikacin in all cases and 97.2% survived at discharge. A percentage of 48 infants was resistant to ampicillin (13). Tullus et al. (14) tested in vitro 13 antimicrobial agents to update the guidelines for empiric therapy of septicemia and meningitis. Ampicillin plus gentamicin provided inadequate empiric therapy for meningitis due to the poor cerebrospinal fluid penetration. Ceftazidime and cefuroxime were moderately active. Cefotaxime provides the best empiric therapy for septicemia and meningitis in infants.

Lepage et al. (15) enrolled 246 children with mean age of 10 months suffering from multiresistant Salmonella typhimurium infection. Of these infants, 159 were treated with cefotaxime and 16 infants (10.5%) died. A total of 87 infants were not treated, and 64 (74%) died. Cefotaxime has a high efficacy in treating systematic infection of multiresistant Salmonella typhimurium. Cefotaxime and ceftriaxone are highly active against Escherichia coli and group B streptococci which were the causative agents in neonatal meningitis (18). Cefotaxime and ceftriaxone are highly active against Escherichia coli and group B streptococci, but not active against Listeria monocytogenes. Penicillin G was more active than ampicillin and piperacillin against group B streptococci.

Fifty children with bacterial meningitis were prospectively randomized to receive cefotaxime (50 mg/kg every 6 hours) or ampicillin and chloramphenicol in standard doses (20). Twenty-three patients received cefotaxime and 27 patients received ampicillin and chloramphenicol. Bacterial isolates were: Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitis, group B streptococci, and Salmonella enteritidis. Haemophilus influenzae isolates were resistant to ampicillin. All strains (100%) were susceptible to cefotaxime and 96% of the children were susceptible to ampicillin-chloramphenicol. No adverse drug reactions or side effects were noted in either groups. Cefotaxime is a safe and effective antibiotic for therapy of meningitis in children.

Group B beta-hemolytic streptococci strains accounted for approximately two thirds of all cases of neonatal meningitis, while bacteria that typically account for meningitis in older groups of neonates (Haemophilus influenzae type B, Neisseria meningitis, and Streptococcus pneumoniae) are infrequent causes of meningitis in neonatal population (21). Penicillin G or ampicillin is preferred to treat group B streptococci, ampicillin is active against Listeria monocytogenes meningitis, and ampicillin plus either an aminoglycoside or cefotaxime is suggested to treat gram-negative infections. For very low-birth-weight neonates, who have been in the nursery for a prolonged period of time, organisms such as enterococci and gentamicin-resistant gram-negative bacilli are the most common pathogens. Empiric combinations of antibiotics for such patients would include ampicillin or vancomycin, plus amikacin or cefotaxime.

Of a total of 1,473 neonates entered in the nursery, episodes of meningitis occurred in 31 neonates. Klebsiella and Serratia marcescens were the main pathogens (22). Imipenem and cefotaxime, are recommended for the empirical antibiotic treatment in infants with a clinical diagnosis of meningitis and sepsis. In patients aged from 0 to 15 years, affected by acute bacterial meningitis, the prevalent pathogens were Streptococcus pneumoniae, Neisseria meningitis, Escherichia coli, Haemophilus influenzae, and Group B streptococci. These bacteria were susceptible to ceftriaxone, cefotaxime, and ciprofloxacin (2).

Antibiotic regimen, based on the "third generation" cephalosporins, notably cefotaxime, were the most common antibiotic used for the treatment of infections caused by the group B streptococci and Escherichia coli which were the most common infecting microorganisms in neonates (24). A total of 85 neonates, aged from 1 to 28 days, were affected by bacterial meningitis (25). The most common causative pathogens were group B beta-hemolytic streptococci, Escherichia coli, Proteus mirablis, Enterobacter cloacae, Chryseobacterium meningosepticum, and Klebsiella pneumoniae. Ampicillin and cefotaxime were the most commonly used antibiotics. This treatment caused a fall in mortality rate, but a sustained high incidence of complications and sequelae were observed.

A total of 256 children suffering from bacterial meningitis were treated with intravenous daily doses of 150 to 200 mg/kg cefotaxime (26). The causative pathogens were Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, enteric gram-negative bacilli, and Staphylococcus species. A total of 240 (93.7%) children were cured. Sterilization of cerebrospinal fluid was obtained in 80% of children after 72 hours of treatment.

Seven neonates suffering from gram-negative bacillary meningitis and sepsis were treated with cefotaxime at a dosage of 150 mg/kg/day intravenously divided every 6 hours (27). The causative organisms were Escherichia coli, Klebsiella pneumoniae and Enterobacter sakazakii. All infants recovered with good neurologic outcome. The sterility of cerebrospinal fluid was obtained after a mean of 3.3 days of therapy. Jacobs and Kearns (30) treated 17 neonates with a single intravenous daily dose of 50 mg/kg cefotaxime. The predominant pathogens were Escherichia coli and Enterobacter cloacae. Survival and complications were 95% and 19%, respectively. Cultures of the cerebrospinal fluid was sterile 24 to 48 hours after the initiation of treatment. Jacobs (1988) treated 17 infants and children, one week to three months old, suffering from gram-negative enteric bacillary meningitis with intravenous 200 mg/kg/day cefotaxime. Seventeen (94.4%) of these patients survived, with a complication rate of 23.5% (4/17). The cerebrospinal fluid was sterile after 24 hours from the initiation of the therapy (31). The purulent meningitis is a life-threatening disease. Cefotaxime was administered intravenously at a daily dose of 90 to 200 mg/kg, with a mean dose of 150 mg/kg/day (32). The number of patients was 28 and were aged from 16 days to 7 years. A 79% of patients were cured and a complete recovery was obtained in 71%.

Haffejee (33) compared the effects of cefotaxime and benzyl-penicillin plus gentamicin in 68 neonatal hospitalized patients suffering from septicemia and meningitis. A cure rate of 94.4% was obtained in neonates treated with cefotaxime compared with 72.2% in neonates treated with benzyl-penicillin plus gentamicin. Cefotaxime should be considered a drug of choice in neonates with life-threatening sepsis and meningitis.

Thirteen children with meningitis caused by Haemophilus influenzae, group B beta-hemolytic streptococcus, Streptococcus pneumoniae, Neisseria meningitides, Escherichia coli, or Pseudomonas aeruginosa were unsuccessfully treated with different antibiotics (34). Intravenous cefotaxime successfully treated these children. Intravenous and intraventricular administration of chloramphenicol and gentamicin were unsuccessful in treating a child infected by Escherichia coli. Intravenous and intraventricular cefotaxime cured this child. Cerebrospinal fluid levels of cefotaxime ranged from 300 to 27,200 µg/ml. The MIC concentrations for cefotaxime against the organisms

commonly causing bacterial meningitis are usually well below 0.25 µg/ml. Sixty neonates suffering from meningitis were enrolled in the Adhikari et al. study (35). Streptococcus agalactiae, Klebsiella pneumoniae and Escherichia coli were the commonest pathogens. All isolates were fully susceptible to cefotaxime. Gram-negative isolates showed resistance to ampicillin, chloramphenicol and sulphamethoxazole-trimethoprim.

Klebsiella pneumoniae isolates were resistant to gentamicin and amikacin. Two most common organisms were pneumococci and Klebsiella. The treatment with cefotaxime resulted in the cure and survival of 85% children (36). Failure of monotherapy was observed in 15% children. Not all gram-negative species isolates that cause meningitis can be successfully treated by cephalosporins.

A total of 831 neonates affected by bacterial meningitis were treated with cefotaxime (37). All cases were susceptible to cefotaxime, and 12% showed intermediate susceptibility to penicillin G and to aminopenicillin.

Staphylococcus aureus, Klebsiella pneumoniae, and Pseudomonas aeruginosa were the causative pathogens in 120 neonates (39). Sepsis was significantly higher in low-birth-weight neonates compared with appropriate-birth-weight neonates ($p < 0.05$). All the isolates were sensitive to amikacin, gentamicin, cefotaxime and ampicillin except Acinetobacter baumanii. This organism was only sensitive towards cotrimoxazole, azithromycin, cefotaxime and ceftazidime.

Acquah et al. (40) cultured 331 blood specimens of neonates. Gram-positive cocci isolates were 32.2% and Coagulase-negative cocci isolates were 28.7%. Staphylococci accounted for 60.9% of the total isolates. Gram-negative rods comprised 39.1% of all isolates with Klebsiella, Escherichia coli, and Salmonella typhi being the most common organisms isolated. Acinetobacter showed 100.0% susceptibility to ceftriaxone and cefotaxime but was resistant (100.0%) to ampicillin, tetracycline and cotrimoxazole. Escherichia coli and Klebsiella were 80.0%, and 91% susceptible to ceftriaxone and cefotaxime, respectively. These findings are consistent with the view that ceftriaxone and cefotaxime are effective agents against gram-negative bacteria. Abdullah et al. (41) observed that Salmonella paratyphi-A accounted for 32.71%, and Salmonella paratyphi-B accounted for 6.9%. The total isolates were 217. These organisms were sensitive to quinolones, ciprofloxacin, ofloxacin and, cefotaxime. A percent of 62.64% of the isolates were multidrug resistant. Ciprofloxacin is a suitable empirical choice in enteric fever cases. Increasing frequency of Salmonella Paratyphi A isolates suggests incomplete coverage employing monovalent vaccine.

A total of 2,182 neonates with sepsis were screened and 389 (17.8%), had positive blood cultures (43). Pseudomonas and Klebsiella were the commonest isolates. The pathogens included Acinetobacter, Staphylococcus aureus, Escherichia coli, Enterobacter, Citrobacter, and Enterococci. In the gram-negative group, best susceptibility was amikacin, followed by other aminoglycosides, and by ciprofloxacin and cefotaxime. Gram-positive organisms were susceptible to erythromycin and ciprofloxacin and above 50% to aminoglycosides. Of all isolates, 83.8% were susceptible to either cefotaxime or amikacin. Initial empirical choice of cefotaxime plus amikacin appears to be rational choice for most cases. Of a total of 1,050 neonates, 527 had sepsis (44).

Staphylococcus, Klebsiella, coagulase-negative Staphylococcus, and Escherichia coli were the leading etiologies. The isolates were most sensitive to

levofloxacin, ofloxacin, cefotaxime, and ceftazidime. Ruess et al. (45) investigated the susceptibility pattern of group B streptococci in 190 neonates. All isolates were susceptible to penicillin, ampicillin, and cefotaxime. These isolates were resistant to erythromycin. These findings show an increasing resistance to macrolide for group B streptococci. Lin et al. (62) assessed the susceptibility in 119 invasive and 227 colonizing strains of group B streptococci isolated from neonates.

All strains were susceptible to penicillin, vancomycin, chloramphenicol, and cefotaxime. A total of 3,885 blood samples, 1,210 stool samples, and 1,283 cerebrospinal fluid samples were assessed to determine the antibiotic susceptibility patterns and genotypes of non-typhi Salmonella (46). Non-typhi Salmonella samples were isolated in 27.8%, 19.8%, and 7.7% of these cultures, respectively. The most frequent serotypes were Salmonella enteric serotype Enteritidis and Salmonella enterica typhimurium. Antibiotic sensitivity testing was done using ampicillin, chloramphenicol, gentamicin, cotrimoxazole, cefuroxime, cefotaxime, amoxicillin-clavulanic acid, and tobramycin. Of 234 isolates, 43 (18.4%) were sensitive to all antibiotics tested and 133 (56.8%) were multidrug resistant. The present results indicate a high proportion of multidrug resistance.

Jacobs et al. (49) evaluated the susceptibility of 16 beta-lactam antibiotics against group B streptococci. Penicillin G and N-formimidoyl thienamycin (MK0787) were the most active agents tested, both having a MIC_{90} of 0.06 µg/ml. Ceftriaxone, cefotaxime, cefamandole, and cefotaxime were active, all having a MIC_{90} of 0.12 µg/ml, and ampicillin, cephalotin, and mezlocillin had a MIC_{90} of 0.25 µg/ml. The MIC_{90} of piperacillin, cefoperazone, and ceftazidime was 0.5 µg/ml; less active were carbenicillin, ticarcillin, cefoxitin, and moxalactam and their MIC_{90}s ranged from 1 and 8 µg/ml. Mulder et al. (50) treated 125 isolates of Escherichia coli from cerebrospinal fluid of neonates suffering from meningitis. The generally recommended initial therapy is ampicillin plus gentamicin. Ampicillin and cefuroxime resistance occurred in neonates who had received antibiotics prophylactically. Bacteria developed increased resistance to commonly used antibiotics (51). One third of the admitted neonates were diagnosed as having neonatal sepsis. Early and late onset sepsis was found in 35.4%, and 25.6%, respectively. Escherichia coli was the main pathogen isolate in both early and onset sepsis. Overall, 77% of the isolates were multidrug-resistant, 60% were gram-positive bacteria and 83.4% were gram-negative bacteria. A 79% of mortality was caused by multidrug resistant organisms.

It is difficult to treat Acinetobacter baumanii infections because of their highly resistant antimicrobial profiles (52). All the Acinetobacter baumanii isolated showed 100% resistant to ampicillin, amoxicillin, cefuroxime, cefuroximine axetil, cefoxitin, cefotaxime, and nitrofurantoin. A 67% or higher resistance of Acinetobacter baumanii was observed to ceftazidime, cefepime, imipenem, gentamicin, ciprofloxacin, and trimethoprim/sulfamethoxazole. The high prevalence of multidrug-resistant Acinetobacter baumanii isolates has severe impact on available treatment choices and this impacts treatment outcomes in healthcare facilities.

Blood culture obtained from 216 neonates with suspected clinical sepsis was assessed by Viswanathan et al. (53). Gram-negative infection was predominant (58/100 cases) mainly caused be enteric gram-negative bacteria. Klebsiella pneumoniae was the most common gram-negative isolate. Gram-negative organisms exhibited 100% resistance to ampicillin, cefotaxime, and ciprofloxacin showed resistance among the

gram-negative bacteria. One-third of neonates who developed culture-positive died. Hammoud et al. (54) investigated the incidence, etiological pattern and the antimicrobial resistance of late-onset neonatal infections over a period of 5 years. The overall incidence was 16.9 episodes per 1,000 live births. The commonest pathogen was coagulase Staphylococcus (35.7%); while Klebsiella was the most common gram-negative bacteria (18.8%). Escherichia coli, Enterococcus and Enterobacter species were each responsible for 6% of all infections. Case fatality was 11.7%. Approximately 24% and 20% of Klebsiella infections were resistant to cefotaxime and gentamicin, respectively, while 28% and 24% of Escherichia coli infections were resistant to cefotaxime and gentamicin, respectively.

Sinha et al. (55) treated Morganella morganii sepsis with cefotaxime. The infants developed persistent ventriculitis by the emergence of a cefotaxime-resistant Morganella morganii variant with depression of its AmpC β-lactamase. The risk of development of resistance to cephalosporins should be considered in the infection caused by Morganella morganii.

Bujdakova et al. (56) investigated the occurrence and transferability of beta-lactam resistance in multiresistant Escherichia coli, Klebsiella species, Enterobacter species, Pantoea agglomerans, Citrobacter freundii and Serratia marcescens strains.

The strains were resistant to ampicillin, cefoxitin, cefotaxime, ceftriaxone, ceftazidime, and aztreonam but were susceptible to cefepime and imipenem. The beta-lactam resistance was due to the production of β-lactamase. Twenty-five isolates expressed transferable extended spectrum β-lactamases, and chromosomal encoded AmpC β-lactamase. A total of 561 stool samples obtained from children aged 1 to 60 months were cultured, and analyzed to identify the bacterial etiology and their antimicrobial resistance (57). A percentage of 33.9 samples were positive for bacterial culture. Escherichia coli, Salmonella species, and Shigella were the majority of the positive cultures. More than two-thirds of the Salmonella isolates were resistant to nalidixic acid, chloramphenicol, cotrimoxazole, gentamicin, ampicillin, while 42% were resistant to cefotaxime. Most of Shigella isolates were susceptible to nalidixic acid and cefotaxime, but resistant to the other antibiotics. Most of the Escherichia coli isolates were resistant to amoxicillin, cotrimoxazole, chloramphenicol, and gentamicin. These findings draw attention to the need of a surveillance system for the containment of anti-microbial resistance. A total of 109 children suffering from pneumococcal meningitis were analyzed by Fiore et al. (58). Pneumococcal isolates from 9% of the children were resistant to cefotaxime. Children were likely to have cephalosporin-nonsusceptible pneumococcal meningitis. Nonsusceptible cefotaxime was associated with increased mortality, prolonged length of intensive care unit stay, requirement of intubation or oxygen, and neurologic deficit.

5- CONCLUSION

In conclusion, cefotaxime is a bactericidal "third generation" cephalosporin and is widely considered the antibiotic of choice for the management of neonatal meningitis and sepsis. The diffusion in tissues and the penetration into the cerebrospinal fluid of cefotaxime are good. The half-life of cefotaxime ranges from 2 to 6 hours. Thus cefotaxime has a short half-life and this antibiotic should be administered every 6 hours to neonates. Cefotaxime is not absorbed by the gastro-intestinal apparatus and must be administered intravenously or intramuscularly. The clearance and distribution of volume of cefotaxime are 0.074 ± 0.03 l/h/kg and 0.461 ± 0.027 l/kg,

respectively. After an intravenous dose of 50 mg/kg cefotaxime every 6 hours to neonates, the trough serum concentration of this antibiotic is 3.66±5.65 µg/ml and 1 hour after the administration, the cefotaxime concentration is 3.72±5.57 µg/ml in the cerebrospinal fluid. The MIC_{50} values (µg/ml) for Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitis are 0.024±0.026, 0.062±0.034, and 0.057±0.088, respectively. Therefore, after the intravenous administration of 50 mg/kg cefotaxime every 6 hours to neonates, the trough concentration of cefotaxime is many times higher than the MIC_{50} values for important microorganisms.

After a daily intravenous dose of 150 or 300 mg/kg cefotaxime to neonates, the cerebrospinal fluid concentration of this antibiotic ranged from 0.499 to 2,829 µg/ml and the sterilization of the cerebrospinal fluid occurred in the first 72 hours of treatment in over 90% of neonates. The infecting agents were Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, enteric gram-negative bacilli and Staphylococcus species. Cefotaxime is active against Neisseria meningitis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella specimens, Staphylococcus, Enterobacter specimens, and Haemophilus parainfluenzae, Pseudomonas aeruginosa, Escherichia coli, Citrobacter freundii, and Klebsiella pneumoniae. The purulent meningitis is a life-threatening disease, and a mean intravenous dose of 150 mg/kg/day cefotaxime cured 79% of patients and a complete recovery was obtained in 71% patients. Cefotaxime is an active antimicrobial agent and is safe and well tolerated in neonates and infants.

6- CONFLICT OF INTERESTS

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8- REFERENCES

1. Neonatal Formulary. Seventh edition. John Wiley and Sons, Limited European Distribution Centre New Era Estate, Oldlands Way Bognor Regis, West Sussex, PO22 9NQ, UK. 2015. pp. 136-37.

2. Melmon and Morrelli's Clinical pharmacology. Melmon KL, Morelli HF, Hoffman BB, Nierenberg DW Eds. Third edition 1992. McGraw-Hill, Inc. New York. Pp. 707-8.

3. Lecour H, Seara A, Miranda AM, Cordeiro J, Sarmento J. Treatment of 160 cases of acute bacterial meningitis with cefotaxime. J Antimicrob Chemother. 1984;14 Suppl B:195-202.

4. Wells TG, Trang JM, Brown AL, Marmer BC, Jacobs RF. Cefotaxime therapy of bacterial meningitis in children. J Antimicrob Chemother. 1984;14 Suppl B:181-9.

5. Young TE, Mangum B. NEOFAX twenty-third edition. Antimicrobials. Montvale NJ 07645, 2010. pp 26-7.

6. Leroux S, Roué JM, Gouyon JB, Biran V, Zheng H, Zhao W, Jacqz-Aigrain E. A Population and Developmental Pharmacokinetic Analysis To Evaluate and Optimize Cefotaxime Dosing Regimen in Neonates and Young Infants. Antimicrob Agents Chemother. 2016;60(11):6626-34.

7. Goldwater PN. Cefotaxime and ceftriaxone cerebrospinal fluid levels during treatment of bacterial meningitis in children. Int J Antimicrob Agents. 2005;26(5):408-11.

8. Kearns GL, Young RA, Jacobs RF. Cefotaxime dosage in infants and children. Pharmacokinetic and clinical rationale for an

extended dosage interval. Clin Pharmacokinet. 1992; 22(4):284-97.

9. Lepage P, Bogaerts J, Kestelyn P, Meheus A. Single-dose cefotaxime intramuscularly cures gonococcal ophthalmia neonatorum. Br J Ophthalmol. 1988;72(7):518-20.

10. Bessler H, Gurary N, Aloni D, Vishne TH, Sirota L. Effect of cefotaxime on cytokine production in newborns and adults in vitro. Biomed Pharmacother. 2000;54(7):410-4.

11. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014;27(1):21-47.

12. Lambert-Zechovsky N, Bingen E, Aujard Y, Mathieu H. Impact of cefotaxime on the fecal flora in children. Infection. 1985;13 Suppl.1:S140-4.

13. Dellagrammaticas HD, Christodoulou C, Megaloyanni E, Papadimitriou M, Kapetanakis J, Kourakis G. Treatment of gram-negative bacterial meningitis in term neonates with third generation cephalosporins plus amikacin. Biol Neonate. 2000;77(3):139-46.

14. Tullus K, Olsson-Liljequist B, Lundström G, Burman LG. Antibiotic susceptibility of 629 bacterial blood and CSF isolates from Swedish infants and the therapeutic implications. Acta Paediatr Scand. 1991; 80(2):205-12.

15. Lepage P, Bogaerts J, Van Goethem C, Hitimana DG, Nsengumuremyi F. Multiresistant Salmonella typhimurium systemic infection in Rwanda. Clinical features and treatment with cefotaxime. J Antimicrob Chemother. 1990; 26 Suppl.A: 53-7.

16. Jacobs RF. Cefotaxime treatment of gram-negative enteric meningitis in infants and children. Drugs. 1988;35 Suppl 2:185-9.

17. Hall MA, Ducker DA, Lowes JA, McMichael J, Clarke P, Rowe D, Gordon A, Cole DS. A randomised prospective comparison of cefotaxime versus netilmicin/penicillin for treatment of suspected neonatal sepsis. Drugs. 1988;35 Suppl.2:169-77.

18. Hoogkamp-Korstanje JA. Activity of cefotaxime and ceftriaxone alone and in combination with penicillin, ampicillin and piperacillin against neonatal meningitis pathogens. J Antimicrob Chemother. 1985;16(3):327-34.

19. Bryan CS, John JF Jr, Pai MS, Austin TL. Gentamicin vs cefotaxime for therapy of neonatal sepsis. Relationship to drug resistance. Am J Dis Child. 1985;139(11):1086-89.

20. Jacobs RF, Wells TG, Steele RW, Yamauchi T. A prospective randomized comparison of cefotaxime vs ampicillin and chloramphenicol for bacterial meningitis in children. J Pediatr. 1985;107(1):129-33.

21. Kimberlin DW. Meningitis in the Neonate. Curr Treat Options Neurol. 2002;4(3):239-48.

22. Al-Harthi AA, Dagriri KA, Asindi AA, Bello CS. Neonatal meningitis. Saudi Med J. 2000;21(6):550-3.

23. Nwadioha SI, Nwokedi EO, Onwuezube I, Egesie JO, Kashibu E. Bacterial isolates from cerebrospinal fluid of children with suspected acute meningitis in a Nigerian tertiary hospital. Niger Postgrad Med J. 2013; 20(1):9-13.

24. Holt DE, Halket S, de Louvois J, Harvey D. Neonatal meningitis in England and Wales: 10 years on. Arch Dis Child Fetal Neonatal Ed. 2001; 84(2):F85-9.

25. Chang Chien HY, Chiu NC, Li WC, Huang FY. Characteristics of neonatal bacterial meningitis in a teaching hospital in Taiwan from 1984-1997. J Microbiol Immunol Infect. 2000; 33(2):100-4.

26. Lecour H, Miranda AM, Nogueira JA, Abreu C. Update on the use of cefotaxime for pediatric meningitis in Portugal. Diagn Microbiol Infect Dis. 1995; 22(1-2):125-7.

27. Naqvi SH, Maxwell MA, Dunkle LM. Cefotaxime therapy of neonatal gram-negative bacillary meningitis. Pediatr Infect Dis. 1985; 4(5):499-502.

28. Riordan FA, Thomson AP, Sills JA, Hart CA. Bacterial meningitis in the first three months of life. Postgrad Med J. 1995;71(831):36-8.

29. Kaplan SL, Patrick CC. Cefotaxime and aminoglycoside treatment of

meningitis caused by gram-negative enteric organisms. Pediatr Infect Dis J. 1990; 9(11):810-4.

30. Jacobs RF, Kearns GL. Cefotaxime and desacetylcefotaxime in neonates and children: a review of microbiologic, pharmacokinetic, and clinical experience. Diagn Microbiol Infect Dis. 1989;12(1):93-9.

31. Jacobs RF. Cefotaxime treatment of gram-negative enteric meningitis in infants and children. Drugs. 1988;35 Suppl 2:185-9.

32. Sow A. Cefotaxime treatment of meningitis in children. J Antimicrob Chemother. 1984;14 Suppl B:191-4.

33. Haffejee IE. A therapeutic trial of cefotaxime versus penicillin-gentamicin for severe infections in children. J Antimicrob Chemother. 1984;14 Suppl.B:147-52.

34. Belohradsky BH, Bruch K, Geiss D, Kafetzis D, Marget W, Peters G. Intravenous cefotaxime in children with bacterial meningitis. Lancet. 1980;1(8159):61-3.

35. Adhikari M, Coovadia YM, Singh D. A 4-year study of neonatal meningitis: clinical and microbiological findings. J Trop Pediatr. 1995;41(2): 81-5.

36. Cherubin CE, Eng RH. Experience with the use of cefotaxime in the treatment of bacterial meningitis. Am J Med. 1986;80(3): 398-404.

37. Bilal A, Taha MK, Caeymaex L, Cohen R, Levy C, Durrmeyer X; Groupe des Pédiatres et microbiologistes de l'Observatoire National des Méningites; Members of the National Reference Center for Meningococci. Neonatal Meningococcal Meningitis In France From 2001 To 2013. Pediatr Infect Dis J. 2016;35(11):1270-72.

38. Xu X, Li C, Wu Q, Zhang J, Huang J, Yang G. Prevalence, molecular characterization, and antibiotic susceptibility of Cronobacter spp. in Chinese ready-to-eat foods. Int J Food Microbiol. 2015; 204:17-23.

39. Shrestha RK, Rai SK, Khanal LK, Manda PK. Bacteriological study of neonatal sepsis and antibiotic susceptibility pattern of isolates in Kathmandu, Nepal. Nepal Med Coll J. 2013;15(1):71-3.

40. Acquah SE[1], Quaye L, Sagoe K, Ziem JB, Bromberger PI, Amponsem AA. Susceptibility of bacterial etiological agents to commonly-used antimicrobial agents in children with sepsis at the Tamale Teaching Hospital. BMC Infect Dis. 2013; 13: 89.

41. Abdullah FE, Haider F, Fatima K, Irfan S, Iqbal MS. Enteric fever in Karachi: current antibiotic susceptibility of Salmonellae isolates. J Coll Physicians Surg Pak. 2012; 22(3):147-50.

42. Chang B, Wada A, Hosoya M, Oishi T, Ishiwada N, Oda M, et al. Japanese Invasive Disease Study Group. Characteristics of group B Streptococcus isolated from infants with invasive infections: a population-based study in Japan. Jpn J Infect Dis. 2014; 67(5):356-60.

43. Bhat YR, Lewis LE, K EV. Bacterial isolates of early-onset neonatal sepsis and their antibiotic susceptibility pattern between 1998 and 2004: an audit from a center in India. Ital J Pediatr. 2011; 37: 32.

44. Ogunlesi TA, Ogunfowora OB, Osinupebi O, Olanrewaju DM. Changing trends in newborn sepsis in Sagamu, Nigeria: bacterial aetiology, risk factors and antibiotic susceptibility. J Paediatr Child Health. 2011;47(1-2):5-11.

45. Ruess M, Müller U, Sander A, Berner R. Antimicrobial susceptibility patterns of Streptococcus agalactiae in a German university hospital. Scand J Infect Dis. 2000;32(6):623-6.

46. Oundo JO, Kariuki S, Maghenda JK, Lowe BS. Antibiotic susceptibility and genotypes of non-typhi Salmonella isolates from children in Kilifi on the Kenya coast. Trans R Soc Trop Med Hyg. 2000;94(2):212-5.

47. Aitmhand R, Moustaoui N, Belabbes H, Elmdaghri N, Benbachir M. Serotypes and antimicrobial susceptibility of group B streptococcus isolated from neonates in Casablanca. Scand J Infect Dis. 2000; 32(3): 339-40.

48. Bradsher RW, Ulmer WC. Beta-lactam antibiotic susceptibility of bacteria responsible for neonatal meningitis. Chemotherapy. 1983; 29(3):213-7.

49. Jacobs MR, Kelly F, Speck WT. Susceptibility of group B streptococci to 16 beta-lactam antibiotics, including new penicillin and cephalosporin derivatives. Antimicrob Agents Chemother. 1982; 22(5): 897-900.

50. Mulder CJ, Bol P, Nabbe AJ, Zanen HC. Susceptibility of 126 isolates of Escherichia coli from the cerebrospinal fluid of neonates to five antibiotics. J Antimicrob Chemother. 1985;15(1):115-8.

51. Awad HA, Mohamed MH, Badran NF, Mohsen M, Abd-Elrhman AS. Multidrug-resistant organisms in neonatal sepsis in two tertiary neonatal ICUs, Egypt. J Egypt Public Health Assoc. 2016;91(1):31-8.

52. Lowings M, Ehlers MM, Dreyer AW, Kock MM. High prevalence of oxacillinases in clinical multidrug-resistant Acinetobacter baumannii isolates from the Tshwane region, South Africa - an update. BMC Infect Dis. 2015;15:521.

53. Viswanathan R, Singh AK, Ghosh C, Dasgupta S, Mukherjee S, Basu S. Profile of neonatal septicaemia at a district-level sick newborn care unit. J Health Popul Nutr. 2012; 30(1):41-8.

54. Hammoud MS, Al-Taiar A, Thalib L, Al-Sweih N, Pathan S, Isaacs D. Incidence, aetiology and resistance of late-onset neonatal sepsis: a five-year prospective study. J Paediatr Child Health. 2012; 48(7):604-9.

55. Sinha AK, Kempley ST, Price E, Sharma BK, Livermore DM. Early onset Morganella morganii sepsis in a newborn infant with emergence of cephalosporin resistance caused by depression of AMPC beta-lactamase production.Pediatr Infect Dis J. 2006; 25(4):376-7.

56. Bujdáková H, Hanzen J, Jankovicová S, Klimácková J, Moravcíková M, Milosovic P, et al. Occurrence and transferability of beta-lactam resistance in Enterobacteriaceae isolated in Children's University Hospital in Bratislava. Folia Microbiol (Praha). 2001; 46(4):339-44.

57. Banajeh SM, Ba-Oum NH, Al-Sanabani RM. Bacterial aetiology and anti-microbial resistance of childhood diarrhoea in Yemen. J Trop Pediatr. 2001; 47(5):301-3.

58. Fiore AE, Moroney JF, Farley MM, Harrison LH, Patterson JE, Jorgensen JH, et al. Clinical outcomes of meningitis caused by Streptococcus pneumoniae in the era of antibiotic resistance. Clin Infect Dis. 2000;30(1):71-7.

59. Aujard Y, Brion F, Jacqz-Aigrain E, Kasse MC, Chretien P, Criqui C, et al. Pharmacokinetics of cefotaxime and desacetylcefotaxime in the newborn. Diagn Microbiol Infect Dis. 1989;12(1):87-91.

60. Kafetzis DA, Brater DC, Kapiki AN, Papas CV, Dellagrammaticas H, Papadatos CJ. Treatment of severe neonatal infections with cefotaxime. Efficacy and pharmacokinetics. J Pediatr. 1982;100(3):483-9.

61. Kearns GL, Jacobs RF, Thomas BR, Darville TL, Trang JM. Cefotaxime and desacetylcefotaxime pharmacokinetics in very low birth weight neonates. J Pediatr. 1989;114(3): 461-7.

62. Lin FY, Azimi PH, Weisman LE, Philips JB 3rd, Regan J, Clark P, et al. Antibiotic susceptibility profiles for group B streptococci isolated from neonates, 1995-1998. Clin Infect Dis. 2000; 31(1):76-9.