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Review Article (Pages: 5023-5041)

Clinical Pharmacology of Ciprofloxacin in Neonates: Effects and Pharmacokinetics

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Abstract

Ciprofloxacin is the most commonly used fluoroquinolone. Ciprofloxacin is prescribed for 1 in 44 Americans. Ciprofloxacin is a broad-spectrum bactericidal antibiotic, effective against both gram-positive and gram-negative bacteria, being especially active against the Enterobacteriacae, including many microorganisms resistant to penicillins, cephalosporins and aminoglycosides, and also is effective against Haemophilus influenzae, penicillinase-producing Neisseria gonorrhea, Campylobacter and Pseudomonas aeruginosa.

Streptococci and pneumococci are weakly inhibited and there is a high incidence of staphylococcal resistance to ciprofloxacin. In neonates, the dose of ciprofloxacin is 10 mg/kg intravenously over 30-60 min infusion, and 20 mg/kg is used to treat Pseudomonas aeruginosa infection. Ciprofloxacin treatment is effective in life-threatening multi-drug resistant Pseudomonas aeruginosa. Ciprofloxacin may be administered by mouth and has a bioavailability of 70% and is mainly recovered unchanged in the urine. Ciprofloxacin is safe and well tolerated in infants.

In neonates, the half-life of ciprofloxacin is 3-4 hours. For meningococcal prophylaxis, give a single dose of 30 mg/kg (up to a maximum of 125 mg) orally. Ciprofloxacin is active against Citrobacter kosery that produces brain abscesses. The mortality rate for meningitis due to Citrobacter kosery is approximately 30%. Third-generation cephalosporins and aminoglycosides failed to prevent the high rates of morbidity and mortality caused by Citrobacter infections.

Ciprofloxacin is the antibiotic treatment option for systemic infection or meningitis caused by Citrobacter kosery. Ciprofloxacin has been used to treat neonatal pneumonia, meningitis, and septicemia and was effective in all cases. The aim of this study was to review the clinical pharmacology of ciprofloxacin in neonates.

Key Words: Ciprofloxacin, Effects, Neonate, Resistance, Safety, Susceptibility.

*Please cite this article as: Maria Pacifici G, Marchini G. Clinical Pharmacology of Ciprofloxacin in Neonates: Effects and Pharmacokinetics. Int J Pediatr 2017; 5(6): 5023-41. DOI: **10.22038/ijp.2017.23193.1952**

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Received date: Mar.28, 2017; Accepted date: Apr.22, 2017

1-INTRODUCTION

Ciprofloxacin is a fluoroquinolone, first patented in 1982, with broad-spectrum activity against many gram-positive and gram-negative bacteria and against microorganisms such as Chlamydia and rickettsiae (although gonococci are becoming progressively more resistant). Ciprofloxacin is a broad-spectrum bactericidal antibiotic with activity against a wide range of infectious microorganisms that can be given by mouth and its bioavailability is about 70% and is mainly eliminated by renal route. A single 20 mg/kg dose can be used to treat cholera. Ciprofloxacin is the first-choice antibiotic to treat meningococcal infection. It is particularly useful in the management of enterobacter and other infections resistant to all cephalosporins and to all aminoglycosides. It is particularly useful in the treatment of pulmonary infections with Pseudomonas aeruginosa and Salmonella. Intravenous administration can be painful and can cause local erythemia and phlebitis unless infused slowly. Ciprofloxacin crosses the placenta and diffuses into most body fluids well, including cerebrospinal fluid (adequate levels > 1.0 µg/ml, have been documented in the cerebrospinal spinal of infants with ventriculitis). In neonates, the steady-state half-life is 3 to 4 hours. Dosage only requires review where there is serious renal or liver dysfunction (1).

Ciprofloxacin is the most commonly used fluoroquinolone at present. It is estimated that in 1989 this drug was prescribed for 1 in 44 Americans. Ciprofloxacin is a broad-spectrum antibiotic, being especially active against the Enterobacteriacae (the enteric gram-negative bacilli), including many microorganisms resistant to penicillins, cephalosporins and aminoglycosides, and is also effective against Haemophilus influenzae, penicillinase-producing Neisseria gonorrhea, Campylobacter and pseudomonades. Of the gram-positive microorganisms, streptococci and pneumococci are only weakly inhibited and there is a high incidence of staphylococcal resistance. Intracellular pathogens, such as Mycobacterium tuberculosis, Mycoplasma, Chlamydia, Legionella and Brucella species are inhibited to a variable extent and there is only low activity against anaerobic bacteria. Clinically the fluoroquinolone are best used for infections with facultative and aerobic gram-negative rods and cocci. Some clinical pharmacologists have suggested, sensibly, that to prevent emergence of resistance, ciprofloxacin should be reserved for microorganisms resistant to other drugs (2).

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; March 2017 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

The following key words "ciprofloxacin effects neonates", "ciprofloxacin pharmacokinetics neonates", "ciprofloxacin safety neonate", "ciprofloxacin susceptibility neonates", "ciprofloxacin dosing neonates", and "ciprofloxacin resistance neonates" were used. In addition, the book Neonatal Formulary (1) was consulted.

3-RESULTS

3-1. Dose

Give 10 mg/kg intravenously over 30-60 min infusion when treating severe infection. A higher dose (15 mg/kg) allows continuation of treatment. Use 20 mg/kg when treating Pseudomonas aeruginosa infection. Give one dose every 12 hours in

the first month of life and every 8 hours in infants older than this (unless the plasma creatinine is over twice the normal value). Treatment is usually continued for 10-14 days (1).

3-2. Meningococcal prophylaxis

Give a single dose of 30 mg/kg (up to a maximum of 125 mg) orally (1).

3-3. Drug interactions

Ciprofloxacin treatment increases the half-life of theophylline and to a lesser extent caffeine. Ciprofloxacin can cause prolongation of the QT and should be avoided in infants with congenital long QT syndrome (1).

3-4. Use

Ciprofloxacin is a broad-spectrum bactericidal antibiotic with activity against a wide range of infectious organism that can be given by mouth. A single 20 mg/kg dose can be used to treat cholera. Ciprofloxacin is now the first-choice antibiotic for protection after contact with a case of meningococcal infection (1).

3-5. Effects of ciprofloxacin in neonates

Yousef et al. (3) hypothesized that prophylactic administration of an appropriate antibiotic following each delayed intensification in children with acute lymphoblastic leukemia would reduce the episodes of fever and bacteremia associated with neutropenia, and reduce both the rate and duration of hospitalization. There were 69 patients who received 194 delayed intensifications (controls were 130 neonates). The rate of hospitalization was 90% in the controls and 58% in the study group ($P < 0.001$). The median hospital stay was 10.1 days for controls and 6.0 for the study group ($P < 0.001$). Intensive care unit admissions were reduced from 12 to 1.5% ($P = 0.02$). The overall rate of proven bacteremia was reduced from 22 to 9% ($p = 0.028$). There were no gram-negative bacteremias in the study group compared to 10 (7.7%) in the controls ($P < 0.001$). Compared to historic controls, patients in this study receiving prophylactic ciprofloxacin had a reduced rate and duration of hospitalization and incidence of gram-negative bacteremia.

Approximately 76% of neonates infected with Citrobacter kosery develop brain abscesses. The mortality rate for meningitis due to Citrobacter species is approximately 30%, and of the infants who survive, more than 80% have some degree of mental retardation (4). Third-generation cephalosporins and aminoglycosides failed to combat this infection. A possible basis for these poor outcomes is failure to apply appropriate pharmacokinetic and pharmacodynamic principles in selecting antibiotics that will achieve adequate concentrations to kill the bacteria in granulocytes within the central nervous system. Based on favorable sensitivity data, penetration into neutrophils and the central nervous system, and favorable toxicity profiles, ciprofloxacin and meropenem would appear to be the most appropriate antibiotic treatment options for systemic infection or meningitis caused by Ciprofloxacin and meropenem should be considered antibiotic treatment options for systemic infection or meningitis caused by Citrobacter kosery.

van den Over et al. (5) reported the use of ciprofloxacin in a preterm boy weighing 1,240 grams suffering from an invasive multiple resistant Enterobacter cloacae infection. The treatment was effective, after other antibiotics failed, and no adverse effects were observed during 3 years of follow up. Ciprofloxacin has been used to treat neonatal pneumonia, meningitis, and septicemia and was effective in all cases. Side-effects were limited to dental dyschromia. Pharmacokinetics of ciprofloxacin were studied in seven preterm infants; intravenous doses ranging from 4 to 40

mg/kg per day revealed adequate serum peak concentrations (0.98-5.7 µg/ml), but trough-peak ratios were high (median ratio 32%), suggesting slower elimination of ciprofloxacin in preterm infants as compared to older children. Cerebrospinal fluid was 0.10-1.45 µg/ml. Ciprofloxacin treatment of preterm or lower birth weight infants may be effective and without severe side effects in infections with bacteria resistant to other antibiotics.

Twelve cases of nosocomial meningitis treated with intravenous ciprofloxacin in doses of 10 to 60 mg/kg/day are described by Krcméry et al. (6). Four neonates were 21 to 28 days old and eight infants were 2 to 6 months old. Six patients presented gram-negative meningitis: Escherichia coli (n = 2), Salmonella enteritidis (n = 1), Acinetobacter calcoaceticus (n = 1), two with two organisms, and (Haemophilus influenzae plus Staphylococcus epidermidis, Acinetobacter spp. plus Staphylococcus epidermidis), and six were attributable to Gram-positive cocci (four Staphylococcus aureus and two Enterococcus faecalis). Ten cases were cured. In two cases, reversible hydrocephalus appeared that responded to intraventricular punctures. In seven children, no neurologic sequelae appeared after a 2- to 4-year follow-up. One neonate had relapse of meningitis 3 months later and was ultimately cured, but developed a sequelae of psychomotor retardation. Follow up varied from 27 months to 10 years. Six infants with a gestational age ranging from 24 to 29 weeks and with a birth weight ranging from 700 to 1,200 grams had received at least two courses of different antibiotics (7). These included ampicillin, gentamicin, netilmicin, cefotaxime, and chloramphenicol. Ciprofloxacin 10 mg/kg/day in two divided doses was given intravenously for 14 days. One infant who had ventriculitis received ciprofloxacin for 21 days. Three infants had periventricular hemorrhages and two developed necrotizing enterocolitis before the institution of ciprofloxacin treatment. There was a short interval between colonization and the onset of systemic infection in the majority. Although Enterobacter cloacae was eradicated in every case, three of six infants died. The causes of death were necrotizing enterocolitis and bronchopulmonary dysplasia. In all infants Enterobacter cloacae had been eradicated four to five days after starting ciprofloxacin.

Acute invasive diarrhea is a potentially serious condition in children. A total of 201 children ages 6 months to 10 years (30% < 1 year; 70% < 3 years) had acute invasive diarrhea. They received either ciprofloxacin suspension (10 mg/kg twice-daily + intramuscular placebo; n = 95) or intramuscular ceftriaxone (50 mg/kg/day + placebo suspension; n = 106) for 3 days in a double blind manner (8). Stool cultures for Shigella, Salmonella, Campylobacter species and diarrheagenic Escherichia coli were assessed on days 1, 2, 3, 4 to 5 and 21$\pm$5. Clinical response and safety were assessed on days 1, 2, 3, 4 to 5 and 21$\pm$5. Leibovitz et al. (8) isolated 127 pathogens from 121 (60%) patients: 73 (57%) Shigella; 23 (18%) Salmonella; 18 (14%) Escherichia coli; and 13 (10%) Campylobacter.

Overall bacteriologic eradication on day 4 to 5 was 99% for Shigella, 77% for salmonella and 77% for Campylobacter, with no difference between the 2 groups. Clinical cure or improvement was observed in 100 and 99% of the ciprofloxacin and ceftriaxone groups, respectively. Serum ciprofloxacin values determined on day 3 of the treatment were higher in the majority of patients than were the minimal inhibitory concentration (MIC_{50}) and MIC_{90} values for the Shigella and Salmonella species isolated. Possible drug-related adverse events occurred in 13 patients [ciprofloxacin, n = 8 (8%);

ceftriaxone, n = 5 (4.7%] and were mild and transient. Joint examination was normal during and after completion of therapy in all patients. Oral ciprofloxacin was as safe and effective as intramuscular ceftriaxone for the empiric treatment of acute invasive diarrhea in ambulatory pediatric patients requiring an emergency room visit.

Belet et al. (9) evaluated the efficacy and acute side effects of ciprofloxacin treatment in newborns who developed nosocomial Pseudomonas aeruginosa infection. Intravenous ciprofloxacin treatment was given to 30 newborns who developed nosocomial Pseudomonas aeruginosa infection as proven by culture antibiogram results. Initial doses of ciprofloxacin of 10 mg/kg/day were given and increased up to 40 mg/kg/day according to clinical response, laboratory and culture results. During therapy, white blood cell counts, urinalysis, liver and renal function tests were performed weekly. All patients were examined daily during treatment for possible symptoms of joint toxicity such as erythemia and swelling. The patients were evaluated by general physical examination, with special attention to joints, 1 week after discharge.

Two of the patients (6.6%) died due to pseudomonas infection, but the bacteria were successfully eradicated in 28 patients (93.4%). Four patients died from other causes. No laboratory abnormality related to ciprofloxacin was observed during treatment. Swelling and hyperemia of the joints were not encountered during treatment and 1-week period after discharge. Ciprofloxacin-resistant Pseudomonas aeruginosa isolates were not grown during the study. Ciprofloxacin treatment is effective in life-threatening multi-drug resistant Pseudomonas aeruginosa infections.

3-6. Safety profile of ciprofloxacin in neonates

Drossou-Agakidou et al. (10) administered ciprofloxacin in a dosage of 10 mg/kg/day in two divided doses to 116 neonates (89 preterm and 27 term neonates), and 100 neonates (88 preterm and 12 term neonates) did not receive ciprofloxacin. The age at entry to the study was 14$\pm$19 days for the ciprofloxacin-treated neonates and 12$\pm$8 days in the control group. Ciprofloxacin administration to neonates with sepsis is not associated with increased risk for hematologic, hepatic or renal dysfunction and is not associated with clinical arthropathy or growth impairment of the treated infants during the first year of life.

Chaudhari et al. (11) conducted a case matched control study to observe the adverse effects of ciprofloxacin used in neonatal septicemia. These authors enrolled 30 neonates with multidrug-resistance septicemia who were treated with intravenous ciprofloxacin for 14 days. Thirty matched neonates with septicemia treated with other antibiotics were enrolled as controls. There was no difference in the mean serum electrolytes, hepatic, renal and hematologic parameters of the two groups. Serial ultrasonographic measurement of the cartilage of the knee after 1 and 6 months showed no difference in the two groups. The femoral cartilage showed an increase of 78.8% in the mean longitudinal area after 6 months in the study group. In the control group, the femoral cartilage showed a 78.4% increase after 6 months. Similarly, the tibial cartilage showed no difference in the percentage increase in size of the study and control groups at the end of 6 months. When controlled for birth weight and gestation, cartilage size was not affected by ciprofloxacin.

Adefurin et al. (12) determined the safety of ciprofloxacin in pediatric patients in relation to arthropathy, and other adverse events and drug interactions. The most frequent adverse events were musculoskeletal adverse events, abnormal

liver function tests, nausea, change in white blood cell counts and vomiting. There were six drug interactions [with aminophylline (n = 4) and methotrexate (n = 2)]. The only drug related death occurred in a neonate who had an anaphylactic reaction. A total of 258 musculoskeletal events occurred in 232 pediatric patients (risk 1.6%, 95% coefficient interval 0.9% to 2.6%). Arthralgia accounted for 50% of these infants. The age of occurrence of arthropathy ranged from 7 months to 17 years (median 10 years). All cases of arthropathy resolved or improved with management. Pooled safety data of controlled trials in this review estimated the risk of arthropathy as 1.57 (95% coefficient interval 1.26 to 1.97). Musculoskeletal adverse event occur due to ciprofloxacin use. However, these musculoskeletal events are reversible with management. It is recommended that further prospective controlled studies should be carried out to evaluate the safety of ciprofloxacin, with particular focus on the risk of arthropathy.

Ahmed et al. (13) ascertained the safety of ciprofloxacin in preterm neonates < 33 weeks gestational age. Long-term follow up was done to monitor the growth and development of preterm infants who were treated with intravenous ciprofloxacin in the neonatal period. Ciprofloxacin was used only as a life-saving therapy in cases of sepsis produced by bacterial agents resistant to other antibiotics. Another group of preterm neonates with septicemia who were not exposed to ciprofloxacin, but effectible treated with other antibiotics and followed up, were matched with cases for gender, gestational age and birth weight and included as a comparison group. Forty-eight infants in the ciprofloxacin group and 66 infants in the comparison group were followed up for a mean of 24.7$\pm$18.5 months and 21$\pm$18.8 months, respectively. No osteoarticular problems or joint deformities were observed in the ciprofloxacin group during treatment or follow up. No differences in growth and development between the groups were found. Ciprofloxacin is a safe therapeutic option for newborn infants with sepsis produced by multiple resistant microorganisms. Ciprofloxacin was evaluated in a double-blind, randomized, controlled study of 257 patients ranging from 0 (i.e., less than 1 year) to 12 years old from 33 geographically diverse medical centers (14). The children received either 0.3% ciprofloxacin ophthalmic solution or 0.3% tobramycin ophthalmic solution. Both test medications were administered topically every 2 hours on days 1 and 2 followed by every 4 hours on days 3 through 7. Eyes were cultured prior to enrollment and again on day 7. Treatment efficacy as determined by microbiological culture data and physicians' judgment of overall resolution was similar for the ciprofloxacin and tobramycin groups. Microbiological eradication was observed in 90.1% of the ciprofloxacin group and 84.3% of the tobramycin group (P = 0.29). Physicians judged 87.0% of the ciprofloxacin patients and 89.9% of the tobramycin patients clinically cured on day 7 (P > 0.5). This study showed that topically applied ciprofloxacin ophthalmic solution is safe and effective in a pediatric population experiencing acute bacterial conjunctivitis.

3-7. Bacteria susceptibility to ciprofloxacin and other antibiotics in neonates

Otter et al. (15) reported the identification and control of an outbreak of a ciprofloxacin-susceptible strain of UK epidemic methicillin-resistant Staphylococcus aureus (EMRA)-15 on a neonatal unit. All neonates were screened for MRSA-15 on admission (MRSA)-15 on admission using ciprofloxacin-containing media which did not detect the outbreak strain. The first identified case was a premature neonate who developed

MRSA-15 bacteremia with associated tibial osteomyelitis and multiple subcutaneous abscesses. The outbreak strain was subsequently identified in the nasopharyngeal secretions of a second child who was not clinically infected. Screening of all patients on the neonatal unity using non-ciprofloxacin-media identified two other colonized neonates. All four patient isolates were EMRSA-15, spa type to 22, Staphylococcal Cassette Chromosome mec (SCCmec) IV, Panton-Valentine leucocidin (PVL) negative, indistinguishable by pulsed field gel electrophoresis and susceptible to all non-β-lactam antimicrobials tested. The outbreak strain was cultured from four of 48 environmental sites in a communal milk-expressing room. Unsupervised movement of mothers to and from the milk-expressing room may have contributed to the outbreak. Control measures included cohort isolation of affected neonates, improved environmental cleaning increased emphasis on hand hygiene and education of mothers. Ciprofloxacin-containing media should be used with caution for MRSA-15 screening in settings where ciprofloxacin-susceptible strains (including community-associated MRSA-15) are increasing in prevalence.

Coagulase-negative staphylococci are major causes of bloodstream infections in very-low-birth weight infants cared in neonatal intensive care units (16). Coagulase-negative staphylococcal blood culture isolates were grown in different phases relevant to biofilm formation: planktonic cells at mid-log phase, planktonic cells at stationary phase, adherent monolayers and mature biofilms and their susceptibilities to conventional antibiotics were assessed. The effects of oxacillin, gentamicin, and vancomycin on preformed biofilms, at the highest achievable serum concentrations were examined. Epiflorescence microscopy and confocal laser scanning were used to confirm the stimulatory effects of antibiotics on biofilm. Most coagulase-negative staphylococcal clinic isolates were resistant to penicillin G (100%), gentamicin (83.3%), oxacillin (91.7%), vancomycin (100%), ciprofloxacin (100%), and rifampicin (79.2%). Bacteria grown as adherent monolayers showed similar susceptibility to their planktonic counterparts at mid-log phase. Isolates in a biofilm growth mode were more resistant to antibiotics than both planktonic cultures at mid-log phase and adherent monolayers; however they were equally resistant or less resistant than planktonic cells at stationary phase. Moreover, for some cell-wall active antibiotics, concentrations higher than MICs were required to prevent the establishment of planktonic cultures from biofilms. Finally, the biofilm-growth of two S. capitis isolated could be enhanced by oxacillin at the highest achievable serum concentrations. Qi et al. (16) conclude that the resistance of coagulase-negative staphylococci to multiply initially remains similar when the bacteria shift from a planktonic growth mode into an early attached mode, then increase significantly as the adherent mode further develops. Furthermore, preformed biofilms of some Coagulase-negative staphylococci (CoNS) are enhanced by oxacillin in a dose-dependent manner.

Infections cause significant mortality and morbidity in neonates, especially the premature ones. Totally, 754 blood cultures were made on 623 neonates. Fifty-eight-infant experienced 85 episodes of bacteremia, with 87 isolates cultured (17). The incidence of bacteremia in the neonatal intensive care unit was 9.31% (58/623) with an incidence density of 10.98/1000 patient-days. The overall mortality rate was 7.22%. The case fatality rate of bacteremia was 20.7% (12/58). The bacterial pathogens encountered, in order of frequency, were coagulase-negative Staphylococcus (29%), Staphylococcus

aureus (22%), and Enterobacter cloacae (17%). All of the gram-positive bacteria were susceptible to vancomicin, while the gram-negative bacteria were susceptible to imipenem, amikacin, and ciprofloxacin. Oxacillin-resistant epidermidis, oxacillin-resistant streptococcus aureus, and multi-drug resistant enterobacteria were leading microorganisms causing bacteremia in the neonatal intensive care unit. It is an endless struggle to combat neonatal infection. Periodic evaluation of bacteremia antibiotic susceptibility is necessary. More judicious selection of antibiotics and rotating antibiotic regimens should be kept in mind to reduce the resurgence of multi-drug resistant strains.

Aurangzeb and Hameed (18) determined the frequency of bacterial isolates from neonatal blood cultures and their susceptibility patterns in hospital-born neonates having sepsis. One hundred and twelve hospital-born neonates presented sepsis. Sixty-seven neonates had positive cultures. Escherichia coli was the commonest organism causing early onset neonatal sepsis (n = 35; 77.1%), followed by Pseudomonas aeruginosa (n = 4: 8.9%), Klebsiella (n = 4; 8.9%) and Staphylococcus aureus (n = 2; 4.4%), respectively. In late onset neonatal sepsis Escherichia coli (n = 19; 77.3%) was the commonest followed by Staphylococcus aureus and Pseudomonas aeruginosa (n = 2; 9% each) and Klebsiella (n = 1; 4.5%). The gram-negative microorganisms showed resistance to commonly used antibiotics, ampicillin (79.3%), amoxicillin (74.6%), and ceftazidime (71.6%), cefotaxime (55.2%), and comparatively low resistance to gentamicin (43.2%), tobramycin (34.3%), imipenem (23.6%), amikacin (22.3%), ofloxacin and ciprofloxacin (11.9%), respectively. Staphylococcus aureus showed almost the same resistance to ampicillin, 75%, and comparatively low resistance to the rest of the antibiotics as compared to the gram-negative microorganisms. Neonatal sepsis is mainly caused by gram-negative microorganisms, which are developing resistance to commonly used antibiotics. Salmonella Worthington is an emerging pathogen and has been implicated in a number of outbreaks of neonatal meningitis and septicemia (19). Over a period of 5 years, a total of 30 strains of this pathogen were isolated from blood and cerebrospinal fluid of neonates suffering from septicemia with or without meningitis. Most of these strains were resistant to the penicillin group of antibiotics, and many were resistant to cefotaxime. Sixty percent of the isolates were resistant to amikacin; 86% were resistant to chloramphenicol, and none were resistant to ciprofloxacin or norfloxacin. Parenteral fluoroquinolone should be included as part of antibiotic therapy in suspected cases of neonatal meningitis due to Salmonella Worthington.

Ureaplasma urealyticum was isolated from the endotracheal aspirates of 39 (21.4%) of 182 neonates with respiratory distress requiring ventilator support (20). Mycoplasma hominis was isolated from one (0.5%) neonate. Bacterial cultures were negative in 123 (67.6%) neonates. Antibiotic susceptibility tests carried out on ten isolates of Ureaplasma urealyticum showed that all the microorganisms were sensitive to erythromycin but resistant to lincomycin and sulfamethoxazole trimethoprim. All, except one, Ureaplasma urealyticum were sensitive to tetracycline and minocycline. Two isolates were resistant to ciprofloxacin. This study showed that Ureaplasma urealyticum was a common microorganism isolated from the endotracheal aspirates of neonates with respiratory distress.

3-8. Bacteria resistance to ciprofloxacin and other antibiotics in neonates

Belet et al. (21) evaluated the efficacy and acute side effects of ciprofloxacin

treatment in newborn infants who developed nosocomial Pseudomonas aeruginosa infection. Intravenous ciprofloxacin treatment was given to 30 newborn infants who developed nosocomial Pseudomonas aeruginosa infection as proven by culture antibiogram results. Intravenous ciprofloxacin was initially administered at doses of 10 mg/kg/day and increased up to 40 mg/kg/day according to clinical response, laboratory and culture results. Two of the infants (6.6%) died due to pseudomonas infection, but the bacteria were successfully eradicated in 28 patients (93.4%). Four patients died from other causes. No laboratory abnormality related to ciprofloxacin was observed during treatment. Swelling and hyperemia of the joints were not encountered during treatment and the 1-week period after discharge. Ciprofloxacin-resistant of Pseudomonas aeruginosa isolates were not grown during the study. Ciprofloxacin treatment is effective in life-threatening multi-drug resistant Pseudomonas aeruginosa infection.

The extent to which antibiotic-resistant bacteria are excreted by humans who have not been exposed to antibiotics is not known. Children, who rarely receive fluoroquinolones, provide opportunities to assess the frequency of fecal excretion by fluoroquinolone-naive hosts of fluoroquinolone-resistant gram-negative bacilli (22). Fresh nondiarrheal stools from children were processed by screening them on agar containing ciprofloxacin to recover ciprofloxacin-resistant gram-negative bacilli. Resistant Escherichia coli isolates were also analyzed for urovirulence-associated loci. Thirteen (2.9%) of 455 stools yielded ciprofloxacin-resistant Escherichia coli (n=7 children), Stenotrophomonas maltophilia (n = 4 children), and Achromobacter xylosoxidans and Enterobacter aerogenes (n = 1 child each). Neither the subjects themselves nor members of their households used fluoroquinolones in the 4 weeks preceding collection. Six of the seven resistant Escherichia coli isolates belonged to phylogenetic groups B2 and D, in which extraintestinal pathogenic Escherichia coli bacteria are frequently found. All resistant Escherichia coli isolates contained at least three putative Escherichia coli virulence loci. Most ciprofloxacin-resistant bacteria were resistant to additional antibiotics. Potentially pathogenetic bacteria that are resistant to therapeutically important antimicrobial agents are excreted by some humans, despite these persons' lack of exposure to the particular drugs. The sources of these resistant organism are unknown. This underrecognized reservoir of drug-resistant potential pathogens poses public health challenges.

Gurnee et al. (23) conducted a prospective cohort study of 80 healthy twins and their mothers to determine the frequency of excretion of ciprofloxacin-resistant, potentially pathogenic Escherichia coli. Stool specimens were cultured selectively for ciprofloxacin-resistant gram-negative bacteria. Isolates were categorized on the basis of additional resistance and virulence profiles. Fifteen children (19%) and 8 mothers (20%) excreted ciprofloxacin-resistant Escherichia coli. Overall, 33% of 40 families had at least 1 member whose stool specimen yielded ciprofloxacin-resistant Escherichia coli on culture. Fifty-seven submitted stool specimens (2.8%) contained such microorganisms; clones Escherichia coli sequence type 131 Sub-clone H30 (ST131-H30) and ST405 accounted for 52 and 5 of the positive specimens, respectively. Length of hospital stay after birth (P = 0.002) and maternal colonization (P = 0.0001) were associated with subsequent childhood carriage of ciprofloxacin-resistant Escherichia coli; antibiotic use, and suppression, sex, mode of delivery, and maternal perinatal

antibiotic use were not. Ciprofloxacin-resistant Escherichia coli were usually resistant to additional antibiotic classes, and all had virulence genotypes typical of Extraintestinal pathogenic Escherichia coli. Healthy children and their mothers commonly harbor ciprofloxacin-resistant Escherichia coli with pathogenic potential.

Beeton et al. (24) examined the prevalence and mechanisms of antibiotic resistance among clinical strains isolated from 95 neonates, 32 women attending a sexual health clinic, and 3 patients under investigation for immunological disorders, between 2007 and 2012 in England and Wales. MICs were compared using broth microdilution method and the Mycoplasma IST2 assay, three isolates carried the tet(M) tetracycline resistance gene (2.3%; confidence interval 0.49 to 6.86%); two isolates were ciprofloxacin resistant (1.5%; confidence interval 0.07 to 5.79%) but sensitive to levofloxacin and moxifloxacin, while no resistance was seen to any macrolides tested. The MIC values for chloramphenicol were universally low (2 µg/ml), while inherently high-level MIC values for gentamicin were seen (44 to 66 µg/ml). The Mycoplasma IST2 assay identified a number of false positive ciprofloxacin resistance, as the method does not conform to international testing guidelines. While antibiotic resistance among Ureaplasma isolates remains low, continued surveillance is essential to monitor trends and threats from importation of resistant clones.

The antimicrobial susceptibilities and prevalence of plasmid-mediated quinolone resistance determinants among Salmonella enterica serotype Typhimurium isolates from hospitalized pediatric patients with diarrhea in China were investigated by Yu et al. (25). In total, 40 (64.5%) of 62 Salmonella Typhimurium isolates were resistant to ciprofloxacin (MIC ≥ 0.5 µg/ml), comprising 28 isolates with low-level resistance and 12 isolates with high-level resistance. All ciprofloxacin-resistant isolates were multiresistant to other antimicrobial agents. Four pulsed-field gel electrophoresis (PFGE) clusters were found amongst the 40 ciprofloxacin-resistant isolates, amongst which PFGE clusters A, B. E and D accounted for 7, 4, 1, and 28 isolates, respectively. Two isolates with high-level ciprofloxacin resistance had two mutations in the quinolone resistance-determining regions (QRDRs) of gyrA and parC. The remaining ciprofloxacin-resistant isolates had only one mutation in the QRDR of gyrA. All 62 Salmonella Typhimurium isolates were negative for pnr and 23 (37.1%) of the isolates were positive for aac(6')-lb-cr. Nineteen isolates harboring aac(6')-lb-cr were found amongst Salmonella Typhimurium isolates in China from hospitalized pediatric patients with diarrhea not receiving quinolones. A single mutation in the QRDR of gyrA as well as production of AAC (6')-lb-cr contributed to ciprofloxacin resistance. Clonal spread was responsible for the dissemination of aac(6')-lb-cr amongst Salmonella Typhimurium.

Wang et al. (26) aimed to correlate the multidrug resistance (MDR) and sequence type (ST) clones of community-associated (CA) methicillin-resistant Staphylococcus aureus (MRSA) to identify the genes responsible for clindamycin and mupirocin resistance in Staphylococcus aureus isolates from pediatric hospitals in mainland China. A total of 435 Streptococcus aureus isolates were collected. Compared with CA methicillin-susceptible Streptococcus aureus (MSSA), the resistance rates of CA-MRSA to ciprofloxacin, chloramphenicol, gentamicin and tetracycline were higher (19.0 versus 2.6%, P<0.001; 14.7 versus 3.1%, P<0.001; 14.7 vversus 3.1%, P<0.01; and 46.0 versus 13.3%, P<0.001, respectively). Compared with hospital-associated (HA)-MRSA, the resistance

rates of CA-MRSA to ciprofloxacin, gentamicin, rifampicin, tetracycline and trimethoprim-sulfamethoxazole were lower (19 versus 94.8%, P<0.001; 14.7 versus 84.4%, P<0.001; 5.5 versus 88.3%, P<0.001; 46 versus 94.8%, P<0.001; and 1.8 versus 9.1%, P<0.01, respectively). The resistance rates of CA-MRSA, HA-MRSA and CA-MSSA to clindamycin (92.0, 77.9 and 64.1%, respectively) and erythromycin (85.9, 77.9 and 63.1%, respectively) were high. The MDR rates (resistance to three or more non-β-lactams) were 49.6, 100% and 14% in the CA-MRSA, HA-MRSA and CA-MSSA isolates, respectively. Five of seven ST clones in the CA-MRSA isolates, namely ST59, ST338, ST45, ST910 and ST965, had MDR rates of >50% (67.9, 87.5, 100, 50 and 83.3%, respectively).

The constitutive phenotype of macrolide-lincosamide-streptogramin B [MLS (B)] resistance (69%) and the ermB gene (38.1%) predominated among the MLS (B)-resistant CA Streptococcus aureus strains. The resistance rate to mupirocin was 2.3% and plasmids carrying the mupA gene varied in size between 23 and 54.2 kb in six strains with high-level resistance as determined by Southern blot analysis. The present study showed that resistance to non-β-lactams, especially to clindamycin, is high in CA-MRSA isolates from Chinese children and that the profile of resistance is related to clonal type. This study revealed distinctive patterns of MLS (B)-resistant genes among CA Streptococcus aureus isolates.

3-9. Pharmacokinetics of ciprofloxacin in neonates

Very little is known about the pharmacokinetics of ciprofloxacin in neonates. Payen et al. (27) characterized the population pharmacokinetics of ciprofloxacin in patients with and without cystic fibrosis ranging from 1 day to 24 years. Patients were divided into four groups according to the treatment schedule. They received ciprofloxacin by intravenous infusion (30 min) or by the oral route. The population parameters were computed for an initial group of 37 patients. The data were analyzed by nonlinear mixed-effect modeling by use of a two-comportment structural models. The interindividual variability in clearance was partially explained by a dependence on age and the patient's clinic status. In addition, a significant relationship was found between weight and the initial volume of distribution. Eighteen additional patients were used for model validation and evaluation of limited sampling strategies. When ciprofloxacin was administered intravenously, sampling at a single point (12 hours after the start of infusion) allowed the precise and accurate estimation of clearance and the elimination, as well as the ciprofloxacin concentration at the end of the infusion. The number of samples collected from each patient ranged from 1 to 12. In newborns (age 0-28 days) the mean clearance, the distribution volume, and the half-life were 0.39 (l/h), 7.19 (l) and 16.6 hours, respectively.

Zhao et al. (28) evaluated the population pharmacokinetic of ciprofloxacin in neonates and young infants < 3 months of age and defined the appropriate dose in order to optimize ciprofloxacin treatment in this vulnerable population. Blood samples were collected from neonates treated with ciprofloxacin. Population pharmacokinetic analysis was performed using NONMEM software. The data from 60 newborn infants with a postmenstrual age ranging from 24.9 to 47.9 weeks were available for population pharmacokinetic analysis. A two-compartment model with first-order elimination showed best fit with data. A covariate analysis identified that gestational age, postnatal age, current weight, serum creatinine concentration, and use of inotropes had a significant

impact on ciprofloxacin pharmacokinetics. Monte Carlo simulation demonstrated that 90% of hypothetical newborns with a postmenstrual age < 34 weeks treated with 7.5 mg/kg twice-daily and 84% of newborns with a postmenstrual age ≥ 34 weeks and young infants receiving 12.5 mg/kg twice-daily would reach the area under the curve/ minimum inhibitory concentration (AUC/MIC) target of 125, using the standard EUCAST MIC susceptibility breakpoint of 0.5 µg/ml. The associated risks of overdose for the proposed dosing regimen were < 8%.

Aggarwal et al. (29) determined the multi-dose pharmacokinetics of intravenous ciprofloxacin in 24 preterm infants with postnatal age < 28 days, who received intravenous ciprofloxacin 10 mg/kg/dose 12 hourly for clinical and/or culture proven sepsis. Of 24 neonates included in the study (mean gestational age 32±2.4 weeks), 3 died and 11 dropped out in the initial few days, leaving 20 neonates whose data on serum ciprofloxacin were available. Peak values on days 1, 3, and 7 were 2.3±0.39 µg/ml, 3.0±0.44 µg/ml, and 2.7±0.39 µg/ml, respectively (P > 0.05). Trough values on differences on these days were 0.7±0.14 µg/ml, 0.8±0.14 µg/ml, and 1.0±0.21 µg/ml, respectively (P > 0.05). There were no differences between the < 1,500 gram birth weight and > 1,500 grams birth weight sub-group and the postnatal age < 7 days and > 7 days sub-groups with respect to the corresponding peak and trough values on days 1, 3, and 7.

The 95% confidence interval of serum concentrations were above the MIC_{90} for most Enterobacteriacae species, however the lower bound of the 95% confidence interval of the mean trough levels was lower than MIC_{90} for Pseudomonas aeruginosa and Staphylococcus aureus. No adverse effects were observed. Intravenous ciprofloxacin in a dose of 10 mg/kg/dose 12 hourly is an effective treatment of neonatal sepsis, but higher doses may be required for treating Staphylococcus aureus and Pseudomonas aeruginosa. The peak and trough serum ciprofloxacin concentrations are summarized in **Table.1**.

Table-1: Peak and trough serum concentrations of ciprofloxacin in neonates. The figures are the mean ± SEM, range, and (95% confidence interval), by Aggarwal et al. (29)

Postnatal days	Peak levels (µg/ml)	Trough levels (µg/ml)
1	2.3±0.39 (1.5-3.1)	0.7±0.14 (0.4-1.0)
Range	0.2-6.8	0.0-2.1
3	3.0±0.44 (2.1-3.9)	0.8±0.14 (0.5-1.1)
Range	0.1-7.1	0.0-2.1
7	2.7±0.39 (1.9-3.5)	1.0±0.21 (0.6-1.4)
Range	0.5-7.1	0.1-3.5

SEM: standard error of the mean.

4-DISCUSSION

Among the fluoroquinolones, ciprofloxacin is the most commonly prescribed drug of this class of antibiotics. In 1989, ciprofloxacin was prescribed for 1 in 44 Americans (2). Ciprofloxacin has a broad- spectrum of activity against many gram-positive and gram-negative bacteria and against microorganisms such as

Chlamydia and rickettsiae. It is particularly useful in the management of enterobacter and other infections resistant to all cephalosporins and all the widely used aminoglycosides. Ciprofloxacin has been used to treat neonatal pneumonia, meningitis, and septicemia and was effective in all cases. Ciprofloxacin treatment is effective in life-threatening multi-drug resistant Pseudomonas aeruginosa, and it is active against Haemophilus influenzae, penicillin-producing Neisseria gonorrhea, Campylobacter and Pseudomonas aeruginosa. Mycobacterium tuberculosis, Mycoplasma, Chlamydia, Legionella and Brucella species are inhibited to a variable extent (2).

Ciprofloxacin is a bactericidal antibiotic which may be given by mouth and its bioavailability antibiotic is 70%, and is mainly excreted unchanged in urine. A single 20 mg/kg dose can be used to treat cholera. Ciprofloxacin is now the first-choice antibiotic for protection after contact with a case of meningococcal infection. In neonates, the dose of ciprofloxacin is 10 mg/kg intravenously over 30-60 min infusion. The half-life of ciprofloxacin is 3-4 hours in neonates (1).

Ciprofloxacin is administered to neonates as a salvage therapy for sepsis due to multi-drug-resistant strains or with signs of clinical deterioration under first-line antibiotic treatment. Initial administration was always intravenous with variable dosing schedule. Clinical response to treatment was estimated at 64% and 91% in two cohort studies, with a median of 83% in case series. No serious adverse events, particularly joint toxicity, were observed, although evaluation was predominantly clinical and follow-up limited to a few months after end of treatment (30). Yousef et al. (3) observed that prophylactic administration of ciprofloxacin following each delayed intensification in children with acute lymphoblastic leukemia would reduce the episodes of fever and bacteremia associated with neutropenia and reduce both the rate and duration of hospitalization. Approximately 76% of neonates infected with Citrobacter kosery develop brain abscesses. The mortality rate for meningitis due to Citrobacter species is approximately 30%. Third-generation cephalosporins and aminoglycosides failed to kill Citrobacter kosery. Based on penetration into neutrophils and the central nervous system, ciprofloxacin and meropenem are considered the antibiotic treatment options for systemic infection or meningitis caused by citrobacter koseri (4).

Ceftazidime (100 mg/kg/day) and tobramycin (5 mg/kg/day) failed to cure a neonate with a diagnosis of unresponsive bacterial meningitis. Ceftazidime (100 mg/kg/day) was substituted and carbenicillin (100 mg/kg/6 hourly) was also added empirically. Treatment with ciprofloxacin was given (10 mg/kg/day 12 hourly), intravenously, 3 days after the infant's admission to hospital, the diarrhea lessened and the seizures and irritability subsided. The ciprofloxacin has provided to be an important antibiotic for neonatal infections. Twelve neonates of nosocomial were treated with intravenous ciprofloxacin (10 to 60 mg/kg/day) (6).

The pathogens were Escherichia coli, salmonella enteritis, Acinetobacter calcoaceticus, Haemophilus influenzae, staphylococcus epidermidis, Acinetobacter species and Staphylococcus epidermidis, Staphylococcus aureus and Enterococcus faecalis. Ten infants were cured. In two cases, reversible hydrocephalus appeared that responded after 2 to 4-year follow up. Acute invasive diarrhea is a potentially serious condition in children (8). Isolated pathogens were Shigella, salmonella, Escherichia coli, and Campylobacter. Oral ciprofloxacin was safe and effective as the intramuscular ceftriaxone for the empirical treatment of acute invasive diarrhea. Belet

et al. (9) evaluated the efficacy and acute side effects of ciprofloxacin treatment in newborns who developed nosocomial Pseudomonas aeruginosa infection. Ciprofloxacin initial dose was 10 mg/kg/day and it was increased up to 40 mg/kg/day. Ciprofloxacin-resistant Pseudomonas aeruginosa isolates were not grown during the study. Ciprofloxacin treatment is effective in life-threatening multi-drug resistant Pseudomonas aeruginosa infections. Ciprofloxacin at the dosage of 10 mg/kg/day in two divided doses to 116 neonates (preterms and terms) is not associated with increased risk for hematologic, hepatic or renal dysfunction and is not associated with clinical arthropathy or growth impairment (10). Chaudhari et al. (11) conducted a case matched control study to observe the adverse effects of ciprofloxacin used in neonatal septicemia. Thirty neonates with multidrug-resistance septicemia were treated with intravenous ciprofloxacin for 14 days. There was no difference in the mean serum electrolytes, hepatic, renal and hematologic parameters in neonates treated with ciprofloxacin and in controls.

The femoral cartilage showed an increase of 78.8% in the mean longitudinal area after 6 months in the ciprofloxacin treated infants, and in the control group the femoral cartilage showed a 78.4% increase. Ciprofloxacin has no effects on cartilage size. Adefurin et al. (12) determined the safety of ciprofloxacin in pediatric patients in relation to arthropathy, and other adverse effects. The most frequent adverse events were musculoskeletal adverse events, abnormal liver function tests, nausea, change in white blood cells and vomiting. The age of occurrence of arthropathy ranged from 7 months to 17 years (median 10 years). Musculoskeletal adverse events occur due to ciprofloxacin use. However, these musculoskeletal events are reversible with management. Ahmed et al. (13) ascertained the safety of ciprofloxacin in preterm infants < 33 weeks gestational age. Ciprofloxacin was used only as a life-saving therapy in cases of sepsis produced by bacterial agents resistant to other antibiotics. Forty-eight infants in the ciprofloxacin group and 66 infants in the comparison group were followed for a mean of 24.7$\pm$18.5 months and 21$\pm$18.8 months, respectively. No osteoarticular problems or joint deformities were observed in the ciprofloxacin during treatment or follow-up. The effects of ophthalmic solution of ciprofloxacin or ophthalmic solution of tobramycin were compared in 256 infants < 1 year old (14). Physicians judged 87.0% of the ciprofloxacin patients and 89.9% of the tobramycin patients clinically cured on day 7. Topically applied ciprofloxacin ophthalmic solution is safe and effective.

Coagulase-negative staphylococci are major causes of bloodstream infections in very-low-birth weight infants cared in neonatal intensive care units (16). Most coagulase-negative staphylococcal clinic isolates were resistant to penicillin G (100%), gentamicin (83.3%), oxacillin (91.7%), vancomycin (100%), ciprofloxacin (100%), and rifampicin (97.2%). Moreover, for some cell-wall active antibiotics, concentrations higher than conventional MICs were required to prevent the establishment of planktonic cultures from biofilms.

Finally, the biofilm-growth of two S. capitis isolates could be enhanced by oxacillin at the highest achievable serum concentrations. Qu et al. (16) conclude that the resistance of coagulase-negative staphylococci to multiple antibiotics initially remain similar when the bacteria shift from a planktonic growth mode into an early attached mode, then increase significantly as the adherent mode further develops. Furthermore, preformed biofilms of some CoNS are enhanced by oxacillin in a dose-dependent manner. Moreover,

for some cell-wall active antibiotics, concentrations higher than conventional MICs were required to prevent the establishment of planktonic cultures from biofilms. Finally, the biofilm-growth of two S. capitis isolates could be enhanced by oxacillin at the highest achievable serum concentration. Qu et al. (16) conclude that the resistance of coagulase-negative staphylococci to multiple antibiotics initially remain similar when the bacteria shift from a planktonic growth mode into an early attached mode, then increase significantly as the adherent mode further develops. Furthermore, preformed biofilms of some CoNS are enhanced by oxacillin in a dose-dependent manner. Infections cause significant mortality and morbidity, especially in prematures. The incidence of bacteremia in the neonatal intensive care unit was 9.31% (17).

The case fatality rate of bacteremia was 20.7%. The bacterial pathogens encountered, in order of frequency, were coagulase-negative Staphylococcus (29%), Staphylococcus aureus (22%), and Enterobacter cloacae (17%). All of the gram-positive bacteria were susceptible to vancomicin, while the gram-negative bacteria were susceptible to imipenem, amikacin, and ciprofloxacin. Oxacillin-resistant S. epidermidis, oxacillin-resistant Streptococcus aureus, and multi-drug resistant enterobacteria were leading microorganisms causing bacteremia in the neonatal intensive care unit.

It is an endless struggle to combat neonatal infection. Periodic evaluation of bacteremia antibiotic susceptibility is necessary. The frequency of bacterial isolates from neonatal blood cultures and their susceptibility pattern in hospital born neonates was determined by Aurangzeb and Hameed (18). Escherichia coli was the commonest microorganism causing early onset neonatal sepsis (77.1%), followed by Pseudomonas aeruginosa (8.9%), and Klebsiella (8.9%). In late onset neonatal sepsis, Escherichia coli was the commonest (77.3%) followed by Staphylococcus and Pseudomonas aeruginosa (9% each) and Klebsiella (4.5%). The gram-negative microorganism showed resistance to commonly used antibiotics. Neonatal sepsis is mainly caused by gram-negative microorganisms, which are developing resistance to commonly used antibiotics. Thirty strains of Salmonella Worthington were isolated from blood and cerebrospinal fluid of infants suffering from septicemia with or without meningitis (19). Most of these strains were resistant to the penicillin group of antibiotics, and many were resistant to cefotaxime, amikacin chloramphenicol, but none were resistant to ciprofloxacin or norfloxacin. Parental fluoroquinolones should be included as part of antibiotic therapy in suspected cases of neonatal meningitis due to Salmonella Worthington.

Intravenous ciprofloxacin was given to 30 newborn infants who developed nosocomial Pseudomonas aeruginosa infection (21). Intravenous ciprofloxacin treatment was initially administrated at doses of 10 mg/kg/day and increased up to 40 mg/kg/day. Ciprofloxacin-resistant of Pseudomonas aeruginosa isolates were not grown during the study. Ciprofloxacin treatment is effective in life-threatening multi-drug resistant Pseudomonas aeruginosa infection. Fresh nondiarrheal stools obtained from children were processed by screening them on agar containing ciprofloxacin to recover ciprofloxacin-resistant gram-negative bacilli (22). The microorganisms isolated were Escherichia coli, Stenotrophomonas maltophilia, Achromobacter xylosoxidans, and Enterobacter aerogenes.

All resistant Escherichia coli isolates contained at least three putative Escherichia virulence loci. Most ciprofloxacin-resistant bacteria were resistant to additional antibiotics.

Potentially pathogenic bacteria are resistant to therapeutically important antimicrobial agents. Stool specimens were cultured selectively for ciprofloxacin-resistant gram-negative bacteria. Fifteen children (19%) and 8 mothers (20%) excreted ciprofloxacin-resistant Escherichia coli (23). Overall, 33% of 40 families had at least 1 member whose stool specimens yielded ciprofloxacin-resistant Escherichia coli on culture. Beeton et al. (24) examined the prevalence and mechanisms of antibiotic resistance among clinical strains isolated from 95 neonates, 32 women, and 3 patients under investigation for immunologic disorders. Three isolates (2.3%) carried the tet (M) tetracycline resistance, 2 isolates (1.5%) were ciprofloxacin resistance but sensitive to levofloxacin and moxifloxacin, while no resistance was seen to any macrolides.

Chmielarczyk et al. (31) investigated the prevalence of plasmid-mediated quinolone resistance (PMQR) determinants in Escherichia coli from infants in neonatal intensive care units [NIUCs]. The study was conducted on 80 Escherichia coli strains isolates from different types of infections. Six (5%) isolates were not susceptible to ciprofloxacin, 16% to ofloxacin and 6.2% to levofloxacin.

Among 80 isolates, 27.5% carried at least one PMQR determinant (n = 22). PMQR-positive isolates had significantly higher ciprofloxacin MICs values (28.8-fold higher when comparing to the MIC_{50}) than the PMQR-negative strains (0.23 versus 0.008 µg/ml), regardless of the presence of quinolone resistant-determining region mutations. These data suggest that the number of pnr genes detected in Escherichia coli from newborns may be related to the selection of pnr through antimicrobial exposure. Even if fluoroquinolones are not commonly used in the NICU, Escherichia coli isolates may carry PMQR. The high prevalence of PMQR is of serious concern, as it may be horizontally transferred to other pathogenic bacteria. The antimicrobial susceptibilities and prevalence of plasmid-mediate quinolone resistance determinants among Salmonella serotype Typhimurium isolates from hospitalized pediatric patients with diarrhea were investigated by Yu et al. (25). In total, 40 (64.5%) of Salmonella Typhimurium isolates were resistant to ciprofloxacin (MIC $\geq$ 0.5 µg/ml), compared to 28 isolates with low-level resistance and 12 isolates with high-level resistance. All ciprofloxacin-resistant isolates were multiresistant to other antibiotics. Wang et al. (26) correlated the multidrug resistance (MDR) and serum sequence type (ST) clones of community-associated (CA) methicillin-resistant Staphylococcus aureus (MRSA) to identify the genes responsible for clindamycin and Staphylococcus aureus isolates from pediatric hospitals. A total of 435 Staphylococcus aureus isolates were collected. Compared with CA methicillin-susceptible Staphylococcus aureus (MSSA), the resistance rates of CA-MRSA to ciprofloxacin, chloramphenicol, gentamicin and tetracycline were higher (19.0 versus 2.6%, p-level < 0.001; 14.7 versus 3.1%, P < 0.001; 14.7 versus 3.1%, P < 0.01; and 46.0 versus 13.3%, P < 0.001, respectively).

Very little is known about the pharmacokinetics of ciprofloxacin in neonates. In newborns (age, 0 to 28 days) the mean clearance, the distribution volume and the half-life were 0.39 (l/h), 7.19 (l) and 16.6 hours, respectively (27). Zhao et al. (28) evaluated the population pharmacokinetics of ciprofloxacin in neonates and young infants < 3 months old and defined the appropriate dose in order to optimize ciprofloxacin treatment in this population. Monte Carlo simulation demonstrated that 90% of hypothetical newborns with a postmenstrual age < 34 weeks treated with 7.5 mg/kg twice-daily and 84% of newborns with a postmenstrual

age ≥ 34 weeks and young infants receiving 12.5 mg/kg twice-daily would reach the AUC/MIC ratio of 125, using the standard EUCAST MIC susceptibility breakpoint of 0.5 µg/ml. The associated risks of overdose for the proposed dosing regimen were < 8%. Aggarwal et al. (29) determined the multi-dose pharmacokinetics of intravenous ciprofloxacin in 24 preterm infants with postnatal age < 28 days, who received intravenous ciprofloxacin 10 mg/kg 12 hourly. Peak values on days 1, 3, and 7 were 2.3±0.39 µg/ml, 3.0±0.44 µg/ml, and 2.7±0.39 µg/ml, respectively (P > 0.05). There were no differences between the < 1,500 gram birth weight and > 1,500 gram birth weight infants. The 95% confidence interval of serum concentrations was above the MIC_{90} for most Enterobacteriacae sepsis, however the lower bound of 95% confidence interval of the mean trough levels was lower than MIC_{90} for Pseudomonas aeruginosa and Staphylococcus aureus. A dose of 10 mg/kg/dose 12 hourly is an effective and safe treatment of neonatal sepsis.

5- CONCLUSION

In conclusion, ciprofloxacin is the most commonly used of fluoroquinolones. In 1989 ciprofloxacin was prescribed for 1 in 44 Americans. Ciprofloxacin has a broad-spectrum activity against gram-negative and gram-positive bacteria. A single 20 mg/kg dose of ciprofloxacin can be used to treat cholera. This antibiotic is the first-choice agent to treat meningococcal infection. Ciprofloxacin may be administered by mouth and its bioavailability is 70%.

The dose of ciprofloxacin is 10 mg/kg in neonates. Ciprofloxacin is mainly eliminated by renal route. In neonates, the ciprofloxacin has a half-life of 3 to 4 hours. This antibiotic is active against microorganisms resistant to penicillins, cephalosporins, and aminoglycosides. Ciprofloxacin has been used to treat neonatal pneumonia, meningitis, and septicemia and was effective in all cases. This antibiotic is effective in life-threatening multi-drug resistant Pseudomonas aeruginosa. Ciprofloxacin is active against Enterobacteriacae, Salmonella, Neisseria gonorrhea, and Campylobacter. Ciprofloxacin reduces the rate and the duration of hospitalization and the incidence of gram-negative bacteremia. Ciprofloxacin is active against Citrobacter kosery. This microorganism develops brain abscesses, and the mortality rate for meningitis is about 30%. Penicillins, third-generation cephalosporins and aminoglycosides failed to kill Citrobacter kosery whereas this bacteria is killed by ciprofloxacin. Ciprofloxacin is a useful and active agent against several pathogens that are resistant to commonly used antibiotics.

6- CONFLICT OF INTERESTS

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

7- ACKNOWLEGMENTS

The authors thank Dr. Patrizia Ciucci and Dr. Francesco Varricchio of the Medical Library of the University of Pisa for retrieving the scientific literature.

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