http:// ijp.mums.ac.ir
Review Article (Pages: 4723-4740)

Clinical Pharmacology of Cefepime in Infants and Children

*Gian Maria Pacifici[1], Giovanna Marchini[1]

[1] Via San Andrea 32, 56127 Pisa, Italy.

Abstract

Cefepime is a fourth-generation cephalosporin which is approved in Europe and in the USA. Food and Drug Administration (FDA) approves cefepime in the treatment of febrile neutropenia. Cefepime is active against gram-negative microorganisms such as Escherichia coli, Haemophilus influenzae, Enterobacter, Klebsiella, Morganella, Neisseria, Serratia, and Proteus species. Cefepime is also active against gram-positive microorganisms such as Streptococcus pneumoniae, Streptococcus agalactiae, and Staphylococcus aureus. Cefepime binds to plasma proteins ≤ 20%, and it is excreted unchanged in the urine. Cefepime distributes widely in body tissues and fluids such as cerebrospinal fluid, bile, bronchial secretions, ascites fluid, and middle ear. In neonates, the half-life of cefepime ranges from 3.59±0.61 and 5.09±1.80 hours, and in adults it is 2.1 (range, 1.3 to 2.4 hours).

The rank order of the top 10 pediatric pathogens was analyzed and the comparative antimicrobial potency of broad-spectrum parenteral cephalosporins was exterminated. The rank order of the top 10 pediatric pathogens was Streptococcus pneumoniae (15.5%) > Haemophilus influenzae (14.6%) > Staphylococcus aureus (13.8%) > Moraxella catarrhalis = coagulase-negative staphylococci (8.0%) > Escherichia coli (7.8%) > Pseudomonas aeruginosa (5.2%) > Klebsiella spp. (4.8%) > Enterococcus spp. (4.7%) > beta-hemolytic streptococci (4.4%). Cefepime is the most active antibiotic among β-lactams. Cefepime is active against Enterobacter species (MIC_{90}), 2 µg/ml; 99.3% susceptible, whereas the susceptibility rates of other broad-spectrum β-lactams (ceftriaxone, ceftazidime and piperacillin-tazobactam), were significantly lower (78.4 to 81.5). Cefepime remains a very potent alternative for the treatment of contemporary pediatric infections. The aim of the present study was to review the clinical pharmacology of cefepime in infants and children.

Key Words: Cefepime, Dosage, Effects, Pharmacokinetics, Resistance.

*Please cite this article as: Maria Pacifici G, Marchini G. Clinical Pharmacology of Cefepime in Infants and Children. Int J Pediatr 2017; 5(4): 4575-99. DOI: **10.22038/ijp.2017.22763.1907**

Corresponding Author:

Gian Maria Pacifici, MD, Via San Andrea 32, 56127 Pisa, Italy.

Email: pacificigm@tiscali.it

Received date: Feb. 12, 2017; Accepted date: Mar.12, 2017

1-INTRODUCTION

Cefepime is a fourth-generation cephalosporin with treatment efficacy equivalent to third-generation cephalosporins (1). Potential advantages include: more rapid penetration through the cell wall of gram-negative pathogens; enhanced stability to hydrolysis by Beta-lactamases (β-lactamases); and enhanced affinity for penicillin-binding proteins. Cefepime distributes widely in body tissues and fluids (i.e. cerebrospinal fluid, bile, bronchial secretions, Ascites fluid, middle ear). Plasma protein binding is low (≤ 20%), and cefepime is primarily excreted unchanged in the urine. Serum half-life in infants older than 2 months of age is approximately 2 hours (2).

Cefepime is used in the treatment of serious infections caused by susceptible gram-negative microorganisms (e.g. Escherichia coli, Haemophilus influenzae, Enterobacter, Klebsiella, Morganella, Neisseria, Serratia, and Proteus species), especially Pseudomonas aeruginosa that is resistant to third-generation cephalosporins. Cefepime is also active against serious infections caused by susceptible gram-positive microorganisms (e.g. Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, and Staphylococcus aureus) (2).

Cefepime is indicated for the empirical treatment of nosocomial infections where antibiotic resistance, owing to extended-spectrum β-lactamases or chromosomally induced β-lactamases are anticipated. Cefepime has superior activity against nosocomial isolates of Enterobacter (3).

Cefepime has broader gram-positive and excellent gram-negative bacteria coverage. It combines anti-microbial activity and an infrequent tendency to develop resistance making it popular for the treatment of infections due to multi-drug resistant organisms (4). It has good efficacy against β-lactamase and extended- spectrum β-lactamase secreting pathogens, and it shows great promise in management of children with severe and nosocomial infections. It possesses superior bactericidal action compared to other cephalosporins, and is a cheaper and safer alternative to carbapenems. It is well-tolerated, but needs dose adjustments in newborns, and in children with renal insufficiency. Cefepime is a valuable antibiotic, but it should be used judiciously as unnecessary, improper and prolonged use may lead to the emergence of cefepime.

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

2-2. Search Terms

The following key words "cefepime effects neonates", "cefepime pharmacokinetics neonates", "cefepime dosage neonates", and "cefepime resistance neonates", were used. In addition, the book NEOFAX by Young and Mangum (2) was consulted.

3-RESULTS

3-1. Uses of Cefepime

Treatment of serious infections caused by susceptible gram-negative microorganisms (e.g. Escherichia coli, Haemophilus influenzae, Enterobacter, Klebsiella, Morganella, Neisseria, Serratia, and Proteus species), especially Pseudomonas aeruginosa that is resistant to third-generation cephalosporins. Treatment of serious infections caused by susceptible gram-positive microorganisms (e.g. Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, and Staphylococcus aureus) (2).

3-2. Dose

Term and preterm infants > 28 days of age give 50 mg/kg per dose every 12 hours. Term and preterm infants aged ≤ 28 days of age, give 30 mg/kg per dose every 12 hours. Meningitis and severe infections due to Pseudomonas aeruginosa or Enterobacter species give 50 mg/kg per dose every 12 hours. Administer via infusion by syringe pump over 30 min, or intramuscularly. To reduce pain at the intramuscularly injection site, cefepime may be mixed with 1% lidocaine without epinephrine (2).

3-3. Incompatibility of Cefepime

Acyclovir, aminophylline, amphotericin B, cimetidine, diazepam, dobutamine, dopamine, enalprilat, erythromycin, lactobionate, famotidine, ganciclovir, magnesium sulfate, metoclopramide, midazolam, morphine, nicardipine, phenytoin, tobramycin, and vancomycin (2).

3-4. Comparison of Cefepime safety and efficacy to different cephalosporins in pediatric patients

Hoffman et al. (5) compared the safety of cefepime and ceftazidime in pediatric oncology patients. A retrospective study included 532 pediatric oncology patients. The outcomes of patients treated with cefepime for suspected serious bacterial infections were compared to those of patients treated with ceftazidime. Primary outcomes included 30 and 90-day all-cause mortality. The demographic and clinical characteristics of 337 patients treated with ceftazidime were similar to those of 195 patients receiving cefepime. Thirty-day and 90-day all causes mortality rates were compared. There were also no differences in infection-related mortality rates, secondary infections, or adverse drug events. Deaths occurring within 30 days of hospitalization were judged to be attributable to infection, but not the result of treatment failure of adverse drug events. Deaths occurring between 30 and 90 days were associated with progressive or new malignancy. Secondary infection was significantly associated with mortality. The use of cefepime in pediatric oncology patients is not associated with increased mortality, when compared to ceftazidime, however the small number of deaths limits the strength of this conclusion. Previous associations between antimicrobial therapy and increased all-cause mortality may have been confounded by patients' demographic characteristics and co-morbid conditions. All-cause mortality may be an insensitive outcome for studies examining the efficacy and safety of these agents.

Cefepime and ceftazidime are cephalosporins used for the treatment of serious gram-negative infections. These cephalosporins are used off-label in the setting of minimal safety data for young patients. Arnold et al. (6) identified all infants discharged from 348 neonatal intensive care units who were exposed to either cefepime or ceftazidime in the first 120 days of life. A total of 1,761 infants received 13,293 days of ceftazidime, and 549 infants received 4,628 days of cefepime. Laboratory adverse events occurred more frequently on days of therapy with ceftazidime than with cefepime (373 versus 341 per 1,000 infant days, $P < 0.001$). Seizures were the most commonly observed clinical adverse event, occurring in 3% of ceftazidime-treated infants and 4% of cefepime-treated infants ($P = 0.52$). Mortality was similar between the ceftazidime and cefepime groups (5% versus 3%, respectively, $P = 0.07$). There was no difference in the adjusted odds of seizure or the combined outcome of mortality or seizures in infants exposed to ceftazidime versus those exposed to cefepime. Cefepime was associated with fewer laboratory adverse events than ceftazidime, although this may have been due to a significant difference in clinical exposure and severity of illness between

the 2 groups. There was no difference in seizure risk of mortality between the 2 groups. A contemporary collection of 12,737 strains from pediatric patients (<18 years) isolated over a 7-year period (1998-2004), from 52 sentinel hospitals in North America was tested to determine the comparative antimicrobial potency of broad-spectrum parenteral cephalosporins and selected comparator agents. The rank order of the top 10 pediatric pathogens was analyzed by Jones et al. (7), who determined the comparative antimicrobial potency of broad-spectrum parenteral cephalosporins and selected comparator agents. Most of the strains (84.1%) were isolated from blood stream or respiratory tract infections. The rank order of the top 10 pediatric pathogens analyzed was Streptococcus pneumoniae (15.5%)>Haemophilus influenzae (14.6%) >Staphylococcus aureus (13.8%) >Moraxella catarrhalis = coagulase-negative staphylococci (8.0%) >Escherichia coli (7.8%) > Pseudomonas aeruginosa (5.2%) >Klebsiella spp. (4.8%) >Enterococcus spp. (4.7%) > beta-hemolytic streptococci (4.4%). Both cefepime and ceftriaxone (MIC_{90}), 1 µg/ml; 93.9% and 93.7% susceptible, respectively, were highly active against Streptococcus pneumoniae.

However, the Streptococcus pneumoniae strains showed reduced susceptibility to ceftazidime (56.6%), as well as penicillin (56.6%) < trimethoprim-sulfamethoxazole (57.1%) < erythromycin (66.2%) < tetracycline (71.4%). β-Hemolytic streptococci showed 100% susceptibility to penicillin, cefepime, and ceftriaxone. Cefepime and ceftriaxone exhibited high activity against oxacillin (methicillin)-susceptible Streptococcus aureus (MIC_{90}, 4 µg/ml; 100% and 99.8% susceptible, respectively, whereas ceftazidime (MIC_{90}, 16 µg/ml) was active against only 86.7% of strains. Haemophilus influenzae strains showed complete susceptibility to cefepime, ceftriaxone, and levofloxacin (MIC_{90}, ≤ 0.5 µg/ml; 100% susceptibility), and 34.0% susceptibility of Haemophilus influenzae and 99.2% susceptibility of Moraxella catarrhalis strains produced β-lactamase. Although, the 3 cephalosporins tested (cefepime, ceftriaxone, and ceftazidime), were very active (98.6 to 99.6% susceptibility) against Escherichia coli, cefepime (99.0% susceptibility), was slightly more active than ceftriaxone and ceftazidime (96.4% and 95.1% susceptibility, respectively) against Klebsiella species. Cefepime was also the most active β-lactam agent tested against Enterobacter species (MIC_{90}, 2 µg/ml; 99.3% susceptibility), whereas the susceptibility rates of other broad-spectrum β-lactams (ceftriaxone, ceftazidime and piperacillin-tazobactam) were significantly lower (78.4 to 81.5).

Against Pseudomonas aeruginosa, imipenem and piperacillin-tazobactam showed the highest susceptibility rates (94.4% and 93.3%, respectively), whereas imipenem and cefepime showed the lowest resistance rates (1.4% and 2.3%, respectively). The present results indicate that cefepime was the most broad-spectrum cephalosporin analyzed and remains a very potent alternative for the treatment of contemporary pediatric infections in North America.

Ninety infants and children were prospectively randomized to receive cefepime (n = 43) or cefotaxime (n = 47) for therapy of bacterial meningitis (8). The two treatment groups were comparable in terms of age, duration of illness before enrollment, history of seizures, clinical status on admission, and etiology. Six (7%) patients died two treated with cefepime and four treated with cefotaxime. Clinical response, cerebrospinal fluid sterilization, development of complications, antibiotic toxicity, and hospital stay were similar for the two treatment regimens. Concentrations of

cefepime in cerebrospinal fluid varied from 55 to 95 times greater than the maximal information coefficient (MIC) required by the causative pathogens. Audiologic and/or neurologic sequelae were found in 16% of the cefepime-treated patients and 15% of the cefotaxime-treated patients examined 2 to 6 months after discharge. Sáez-Llorens et al. (8), conclude that cefepime is safe and therapeutically equivalent to cefotaxime for management of bacterial meningitis in infants and children. Sarashina et al. (9) compared the efficacy and safety of cefepime and cefozopran empirical monotherapy in pediatric cancer patients with febrile neutropenia. A total of 64 patients with 224 episodes of febrile neutropenia were assigned to receive antibiotic therapy with cefepime (100 mg/kg/day) or cefozopran (100 mg/kg/day). Of these episodes, 223 were considered eligible for the study. Success was defined as resolution of febrile episodes and clinical signs of infection within 120 hours following the start of antibiotic therapy. The success rate was not significantly different between cefepime (56.3%) and cefozopran (64.0%) groups (P = 0.275). Duration of fever, duration of antibiotic, and the success rate in patients with blood stream infection did not differ between the two groups. There was no infection-related mortality in the study period. Both cefepime and cefozopran as monotherapy have satisfactory efficacy and are well tolerated as initial empirical therapy for pediatric cancer patients with febrile neutropenia.

3-5. Extended-infusion of Cefepime in pediatric patients

A prospective, descriptive study of hospitalized patients receiving cefepime following implementation of the extended-infusion dosing strategy as standard of care at a tertiary care children's hospital was reported by Nichols et al. (10). A total of 150 patients were included in the study, with a median age (interquartile range of 6 years (2 to 12.3 years) and median weight interquartile range of 20.7 kg (13.2 to 42.8 kg); 143 (95.3%) patients received cefepime via extended infusions, and 10 (7.0%) patients of those were changed to a 30 min infusion during treatment. The most common reasons for infusion time change were intravenous incompatibility and intravenous access concerns, responsible for 50% of changes. Cefepime intravenous doses of 50 mg/kg over 30 min every 12 and 8 hours achieved probabilities of target attainment of only 15% and 79%, respectively, for Pseudomonas aeruginosa isolates, with MIC 8 µg/ml (11). However, when cefepime was administered over 3 hours, probabilities of target attainment increased to 57% and 100% with every 12- and every 8-hour dosing, respectively, for Pseudomonas aeruginosa isolates (11).

Despite the potential to optimize the pharmacodynamics of cefepime in children as well as data suggesting tolerability, efficacy, and improved clinical outcomes in adults extended-infusion cefepime has not been studied in hospitalized children (12, 13). One reason may be that extended-infusion β-lactam dosing is not feasible in children; however Nichols et al. (14), demonstrated the feasibility of extended-infusion piperacillin/tazobactam in pediatric population with 92% of patients continuing on an extended-infusion piperacillin/tazobactam regimen. Dosing errors and reported incidents during the therapy were sparse (n=12; 8.0%), and were most commonly related to renal dosing errors and/or initial dose error by the prescriber. Because 93.0% of patients who received extended-infusion cefepime remained on extended-infusion cefepime, implementation of extended-infusion cefepime as the standard dosing strategy was feasible in the pediatric patients. Extended-infusion-cefepime was initiated in 95.3% (143/150) of patients, whereas 4.7% (7/150) initially received the 30 min

infusion. Most patients received every-8-hour dosing intervals, but 10 patients received different intervals because of adjustment for impaired renal function. In all, 143 patients (93%) remained on extended-infusion-cefepime throughout the duration of the cefepime course. Also, 15 patients had the infusion time changed from 30 min to 4 hours. Walker et al. (12), conducted a systematic review of available data on the use of extended or continuous infusion of β-lactam and monobactam therapy in the pediatric population (aged 0 to 18 years). The literature search was performed using PubMed, International Pharmaceutical Abstract, and Web of Science. Randomized controlled clinical trials, pharmacokinetic/pharmacodynamic studies, observational studies, and case reports involving pediatric patients who received extended or continuous infusion of β-lactam or monobactam antibiotics were reviewed. One randomized controlled clinical trial, 5 pharmacokinetic studies, 2 pharmacodynamic studies using Monte Carlo simulation, 1 case series, and 7 case reports, were included in the analysis. The cephalosporin class has been studied the most and currently represents the only clinical trial using a continuous- infusion dosing strategy in pediatric patients.

There is limited clinical evidence available to support the use of extended or continuous infusion of β-lactam antibiotics in the pediatric population. Pharmacodynamic studies conducted in this population mirror the current evidence in adults for cefepime and meropenem. The single prospective clinical trial using continuous infusion of ceftazidime failed to demonstrate any clinical benefit over traditional dosing; however, there was equal efficacy. More well-designed prospective clinical trials are required to determine the role of extended or continuous infusion of β-lactam antibiotics in treatment of pediatric patients.

3-6. Antimicrobial susceptibility of Cefepime and comparison to different cephalosporins in pediatric patients

The Canadian Ward Surveillance Study assessed the antimicrobial susceptibility of a variety of available agents against 15,644 pathogens isolated from patients in Canadian hospitals between 2007 and 2009 (15). The most active (based on MIC data) agents against methicillin-resistant Staphylococcus aureus and vancomicin-resistant enterococci were daptomycin, linezolid, tigecycline, and vancomycin (methicillin-resistant Staphylococcus aureus only) with MIC_{90}s (μg/ml) of 0.25 and 2, 2 and 2, 0.5 and 0.12, and 1, respectively. The most active agents against extended-spectrum β-lactamase-producing Escherichia coli were colistin (polymyxin E), meropenem, ertapenem and doripenem, and tigecycline with MIC_{90}s (μg/ml) of 1, ≤ 0.12, 0.25, ≤ 0.12 and 1, respectively. The most active agents against Pseudomonas aeruginosa were amikacin, cefepime, ceftazidime, colistin, doripenem, meropenem and piperacillin-tazobactam, respectively with MIC_{90}s (μg/ml) of 32, 16, 32, 2, 4, 8, and 64, respectively. Overall, the most active agents versus gram-positive cocci from Canadian hospitals were vancomycin, linezolid, cefepime, doripenem, ertapenem, meropenem, piperacillin-tazobactam, and tigecycline (excluding Pseudomonas aeruginosa).

The objective of the study by Sharma et al. (16) was to determine the causative bacteria and pattern of susceptibility to antibiotics in a neonatal intensive care unit of a tertiary care centre, which in turn may help in the implementation of empirical therapy. A total of 364 cases of suspected sepsis were admitted to neonatal intensive care. Of these, 137 cases were positive for culture. The most common organism isolated was Staphylococcus aureus (37.22%) followed by Klebsiella pneumoniae (27.01%) and Escherichia coli

(19.70%). Other organisms which were much fewer in number, which included pathogenic Streptococci, Coagulase negative Staphylococci, Pseudomonas, Acinetobacter species and Enterobacter species. The gram-positive organisms except Streptococci displayed a high level of resistance to most penicillins and ciprofloxacin, but were sensitive to vancomycin, amikacin and cefepime. There was a high incidence of resistance noted with ampicillin, gentamicin and ciprofloxacin amongst most gram negative organisms where cefepime, amikacin and meropenem were effective in most cases.

Growing antimicrobial resistance among community-acquired and hospital pathogens is making the treatment of most of these increasingly difficult. The aim of Dzierzanowska-Fangrat et al. (17), was to determine the antimicrobial susceptibility of the most frequent aerobic microorganisms isolated from children with intraabdominal infections. MICs of piperacillin, piperacillin-tazobactam, cefotaxime, ceftazidime and cefepime were determined by E-test. Piperacillin-tazobactam was the most active agents against Enterobacteriacae and Pseudomonas aeruginosa, inhibiting 92% and 78% of isolates, respectively (17). Susceptibility of Enterobacteriacae to cefotaxime, ceftazidime, and cefepime was 73%, 73% and 87%, respectively, and susceptibility of Pseudomonas aeruginosa to both ceftazidime and cefepime was 76%. Extended-spectrum β-lactamases were detected in 56% Klebsiella species and 11.5% Escherichia coli, but the vast majority of these isolates remained susceptible to piperacillin-tazobactam (MIC_{90} = 12 µg/ml and MIC_{90} = 1 µg/ml, respectively).

Occurrence and transferability of β-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, are presented by Bujdakova et al. (18). The strains were resistant to ampicillin (n = 30), cefoxitin (n = 22), cefotaxime (n = 30), ceftriaxone (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 β-lactam resistance was due to production of β-lactamase and ceftazidime proved to be a stronger β-lactamase inductor than ceftriaxone. Twenty-five clinical isolates expressed transferable extended spectrum β-lactamases, and chromosomally encoded AmpC β-lactamase.

Febrile neutropenia is a common complication of cancer treatment associated with significant morbidity and mortality and the institution of broad-spectrum antibiotic treatment reduces mortality (19). Naseem et al. (19), checked the effectiveness of ticarcillin/clavulanate versus cefepime as monotherapy in febrile neutropenia in lymphoma infants, and also checked the tolerability profile of both drugs. These authors assigned 107 neutropenic infants to receive either cefepime or ticarcillin/clavulanate. The age of neonates ranged from 0 to 19 days (n = 3), 20 to 39 days (n= 45), 40 to 59 days (n = 43), and 60 to 65 days (n = 16).

The study was a prospective, open, randomized controlled trial. Included were all febrile neutropenic infants who had been treated with conventional chemotherapy for a primary, refractory or relapsed lymphoma. Cefepime was administered intravenously at the dose of 2 grams every 8 hours or ticarcillin/clavulanate at a dose of 3.2 grams every 6 hours for empirical monotherapy in febrile neutropenia. For statistical analysis, two tailed Fisher's exact test and Chi-square's test were used to compare the difference in proportion

between groups and response rate. Differences between medians were analyzed by Mann-Whitney U test. Fifty infants were randomly assigned in cefepime group and 52 infants in the ticarcillin/clavulanate group. The overall response rate to therapy was compared in the two groups on day 7 after start of therapy. A successful outcome was reported in 16 (31%) out of 52 infants in ticarcillin/clavulanate group compared to 28 (51%) out 55 infants in the cefepime group (P = 0.35). Overall good response rate was statistically significant in both groups with 31% in cefepime and 51% in ticarcillin/clavulanate group (P = 0.035). All 107 infants enrolled in the study were evaluated for adverse experience on day 7 after initiation of therapy. 17 infants in the ticarcillin/clavulanate group and 23 infants in cefepime group (P < 0.265) faced adverse reaction considered possibly, probably or definitely related to study drugs. Use of cefepime in combination or alone in febrile neutropenia is approved by Food and Drug Administration (FDA).

Cefepime and ticarcillin/clavulanate are not equally effective in the management of febrile neutropenia in lymphoma patients with low to moderate neutropenia. Safety data in both treatment arms was comparable. Cefepime seems to be more efficacious than ticarcillin/clavulanate and may be associated with lesser requirement of aminoglycoside, glycopeptides or both. Safety profile of cefepime is comparable to ticarcillin/clavulanate with slightly more side effects in the cefepime arm.

3-7. Antimicrobial resistance to Cefepime and comparison to different cephalosporins in pediatric patients

De Araujo et al. (20), aimed to verify if restriction of cefepime, the most frequently used cephalosporin in neonatal intensive care unit would ameliorate broad-spectrum susceptibility of gram-negative isolates. Nine hundred and ninety-five premature and term newborn infants were divided into 3 cohorts, according to the prevalence of cefepime used in the unity. Group 1 (n = 396), comprised infants from January 2002 to December 2003, period in which cefepime was the most used broad-spectrum antibiotic. Infants in group 2 (n = 349), were admitted when piperacillin/tazobactam replaced cefepime (January to December 2004), and in group 3 (n = 250), when cefepime was reintroduced (January to September 2005). Meropenem was the alternative third-line antibiotic for all groups. Multiresistance was defined as resistance to 2 or more unrelated antibiotics, including necessarily a third or fourth-generation cephalosporin, piperacillin/tazobactam or meropenem. Statistics involved Kruskal-Wallis, Mann-Whitney and logrank tests, and Kaplan-Meier analysis. Groups were comparable in length of stay, time of mechanical ventilation, gestational age and birth weight. Ninety-eight gram-negative isolates were analyzed. Infants were more likely to remain free of multiresistant isolates by Kaplan-Meier analysis in group 2 when compared to group 1 (P = 0.017), and group 3 (P = 0.003). There was also a significant difference in meropenem resistance rates. Cefepime has a greater propensity to select multiresistant gram-negative pathogens than piperacillin/tazobactam and should not be used extensively in neonatal intensive care.

The antibiotic resistance pattern was used to characterize the isolates, and a retrospective observational study was performed to assess the relationship between antimicrobial use and bacterial resistance. The study was conducted during a 1-year and 7-month period in a 1,500-bed tertiary care hospital in Anhui, China. An Escherichia coli infection was diagnosed in 1.4% of patients (519/36,179) admitted to the hospital between March 1, 1999 and August 31, 2000 (21). Of the 519 isolates, 489 (94.2%), were resistant to at

least one antimicrobial; 86% were resistant to ampicillin, 85% to cephalotin, 83% to piperacillin, 77% to ampicillin/sulbactam, 72% to trimethoprim/sulfamethoxazole, 70% to ciprofloxacin, 61% to cefoperazone, 58% to tobramycin, 56% to gentamicin, 48% to ticarcillin-clavulanate, 44% to cefazolin, 43% to cefuroxime, 36% to cefoxitin, 32% to cefepime, 29% to aztreonam, cefetaxime and ceftriaxone, 28% to ceftazidime, 19% to piperacillin/tazobactam, 10% to amikacin, while all strains tested were susceptible to imipenem. Prior receipt of antimicrobial therapy was significantly associated with infection caused by a resistant organism.

The pattern of antibiotic resistance amongst gram-negative bacteria in pediatric units, which have heavy empirical usage of broad-spectrum antibiotics, was studied prospectively over a 6-month period. A total of 200 consecutive, non-duplicate gram-negative isolates were obtained from 109 patients admitted to intensive care and oncology units in two hospitals (22). The commonest isolates were Klebsiella species (36.5%), and Pseudomonas aeruginosa (20.0%). The isolates showed lower susceptibility rates to the third-generation cephalosporins (47 to 62%) compared with cefepime (91%), imipenem (90%) and ciprofloxacin (99%). Fifty-four (52.8%) Klebsiella and Escherichia coli isolates were determined to be extended-spectrum β-lactamase producing strains. Antibiotics found to be effective against β-lactamase third-generation cephalosporins is a likely consequence of heavy empirical usage of this group of antibiotics. The carbapenems and quinolones remain useful agents in the management of patients admitted to these units.

The rates of multidrug-resistant, extensively drug-resistant and pandrug-resistant isolates amongst non-fermenting gram-negative bacilli, particularly Pseudomonas aeruginosa, have risen worldwide. The clinical consequence of resistance and the impact of adverse treatment on the outcome of patients with Pseudomonas aeruginosa bacteremia remain unclear. To better understand the predictors of mortality, the clinical consequence of resistance and the impact of inappropriate therapy, Dantas et al. (23) analyzed the first episode of Pseudomonas aeruginosa bacteremia in patients from a Brazilian tertiary-care hospital during the period from May 2009 to August 2011.

Antimicrobial susceptibility testing was conducted; phenotypic detection of metallo-β-lactamase and Polymerase chain reaction (PCR) of metallo-β-lactamase genes were performed on carbapenem-resistant strains. Amongst the 120 Pseudomonas aeruginosa isolates, 45.8% were resistant to carbapenem and 36 strains were tested for metallo-β-lactamase detection. A total of 30% were phenotypically positive and, of these, 77.8% expressed as metallo-β-lactamase gene, bla (SPM-1) (57%) and bla (VIM-type) (43%). The resistance rates to ceftazidime, cefepime, piperacillin/tazobactam, carbapenem, fluoroquinolone, and aminoglycoside were 55%, 42.5%, 35%, 45.8%, 44% and 44%, respectively. A total of 30% were phenotypically positive and 77.8% expressed a metallo-β-lactamase gene, bla (SPM-1) and bla (VIP-type) (43%).

Previous antibiotic use, length of a hospital stay ≥ 30 days, prior Pseudomonas aeruginosa, haemodialysis, tracheotomy, pulmonary source of bacteremia and intensive care unit admission were common independent risk factors for antimicrobial resistance. Cefepime resistance, multi-drug resistance and extensive drug resistance were independently associated with inappropriate therapy, which was an important predictor of mortality, being synergistic with the severity of the underlying disease.

The β-lactam susceptibility phenotypes, was documented for all Salmonella enterica serovar Oranienburg expended-spectrum β-lactamase-producing strains. These strains were resistant to ampicillin, cefotaxime, cefepime, and aztreonam (24). They appeared to be partially susceptible to cefetaxime and were susceptible to imipenem and cefoxitin. These results corresponded well with the resistance phenotype conferred by the CTX-M-type of expended-spectrum β-lactamase-producing in Salmonella species. These strains were susceptible to ciprofloxacin, amikacin, trimethoprim plus sulfamethoxazole, and chloramphenicol. All the isolates displayed coresistance to gentamicin and netilmicin. Cefepime resistance, multidrug resistance and extensive drug resistance were independently associated with inappropriate therapy, which was an important predictor of mortality, being synergistic with the severity of the underlying disease.

3-8. Population pharmacokinetics of Cefepime in neonates and children

The pharmacokinetic parameters of cefepime in the various articles reported in this review are summarized in **Table.1**. Monte Carlo simulations performed using the final population to 34 weeks, were included at 1, 7, 14 and 28 days of age. Various doses and dosing intervals, such as 30 or 50 mg/kg and every 6 to 12 hours were tested. Standard and extended duration of infusion (30 min and 3 hours, respectively), were also assessed. The primary pharmacokinetic target for cefepime is percent time above MIC. A 20% plasma protein binding to calculate free cefepime was used. The Clinical and Laboratory Standards Institute revised cefepime break points for Enterobacteriacae in 2014, and MICs of 4 and 8 (μg/ml) were reclassified as susceptible-dose dependent. Pediatric dosing to provide therapeutic concentrations against susceptible-dose dependent organisms has not been defined. Cefepime pharmacokinetic data from published pediatric studies were analyzed. Population pharmacokinetics parameters were determined using NONMEM, and Monte Carlo simulations were performed to determine an appropriate cefepime dosage regimen for susceptible-dose dependent organisms in children. A total of 664 cefepime plasma concentrations from 91 neonates, infants, and children were included in this analysis. The median patient age was 1 month (interquartile range [IQR], 0.2 to 11.2 months). Serum creatinine concentration and postmenstrual age were covariates in the final pharmacokinetics model. Simulations indicated that cefepime dosing at 50 mg/kg every 8 h (as 0.5-h intravenous infusions) will maintain free-cefepime concentrations in serum of > 4 and 8 μg/ml for > 60% of the dose interval in 87.1% and 68.6% of pediatric patients (age, ≥30 days), respectively; and extending the intravenous infusion duration to 3 hours results in 92.3% of patients with free-cefepime levels above 8 μg/ml for > 60% of the dose interval. Cefepime clearance is significantly correlated with postmenstrual age and serum creatinine concentration.

A dose of 50 mg/kg of cefepime every 8 to 12 h does not achieve adequate serum exposure for older children with serious infections caused by gram-negative bacilli with a MIC of 8 μg/ml. Extended intravenous infusions may be useful for this population. Shoji et al. (25) considered 60% free cefepime to represent a conservative target, reflecting nearly maximal bactericidal effects in an animal model, which was appropriate for a pediatric patient population with some degree of immune compromise, such as neonates. Monte Carlo simulations were performed with 2,000 replications for each of the 59 different post-neonatal/gestational combinations

(118,000 virtual subjects in total). The clearance/kg correlated well with the patient's serum creatinine (r = 0.76) and postmenstrual age (r = 0.77). The age-dependent increase in clearance reached a plateau around 2 to 3 years of age. A negative relation (r = -0.76) was found between gestational age and the distribution volume at steady-state.

Lima-Rogel et al. (26), administered cefepime at a dose of 50 mg/kg as an intermittent 30-min infusion; dosing intervals were 8 or 12 hours. Blood sampling was carried out once steady-state blood levels of cefepime were achieved; that is, after five to six doses had been administered. Three blood samples were drawn from each infant, according to the dosing interval that was indicated. For infants with an 8-hours dosing interval, samples were drawn at 0.5 (peak concentration), 4 and 8 hours (trough concentration) post-dose administration. For infants with 12-hours dosing interval, samples were drawn at 0.5, 6, and 12 hours post-dose administration.

Population pharmacokinetic development study was based on 31 neonates. The gestational age, the post-natal age, and the body weight at the time of sampling were 31.7±2.7 weeks, 21.8±14 days, and 1,400±400 grams, respectively. The mean values obtained for cefepime clearance and distribution volume with the simplest basic model were 0.093 l/h and 0.49 l, respectively. There is a positive relationship between cefepime clearance and a subject's calculated creatinine clearance, as expected, because cefepime is a drug that is primarily excreted by the kidneys and the clearance of creatinine estimates the maturity of renal function. Newborn infants tend to eliminate more slowly than older subjects because of immaturity in renal function (1). Preterm infants usually require lower doses or larger dosing intervals compared with term infants to maintain similar steady-state drug blood concentrations (27). Creatinine clearance affects cefepime elimination linearly. Capparelli et al. (28), found a linear relationship between cefepime clearance and serum creatinine concentrations in premature and term infants younger than 4 months of age.

Capparelli et al. (28) administered 50 mg/kg cefepime infused every 30 min every 12 hours to 54 infants. Forty-two infants had a gestational age < 36 weeks and 12 infants had a gestational age ≥ 36 weeks. The postnatal age was < 14 days in 22 infants with a gestational age < 36 weeks, and 20 infants with a postnatal age ≥ 14 days had a gestational age < 36 weeks. Eleven infants with postnatal age ≥ 14 days had a gestational age ≥ 36 weeks and 1 infant with postnatal age ≥ 14 days had a gestational age ≥ 36 weeks. The gestational age at birth was 30.5±5.3 weeks, and the postnatal age was 14.5±14.7 days. Population pharmacokinetic parameters were determined using the program NONMEM.

The distribution volume for infants with a post-conceptional age < 30 weeks was larger than that for infants with a post-conceptional of > 30 weeks (0.51 versus 0.39 l/kg, respectively). The Bayesian analysis-predicted cefepime trough concentration at a dose of 50 mg/kg every 12 hours for infants ≤ 14 days of age was 29.9±16.6 µg/ml. Overall, cefepime was well tolerated in infants who received a single dose to treat infection. Cefepime, dosed at 30 mg/kg/dose every 12 hours for infants < 14 days of age, regardless of the gestational age, should provide antibiotic exposure equivalent to or greater than 50 mg/kg every 8 hours in older infants and children. The pharmacokinetic characteristics of cefepime were determined after the first dose (n = 35), and again under steady-state conditions (n = 31) with a group of 37 infants and children. In eight subjects, a cefepime dose given by intramuscular injection was

substituted for an intravenous dose, and disposition characteristic were studied again. Study subjects ranged in age from 2.1 months to 16.4 years, and all had normal renal function (29). Each patient received 50 mg/kg cefepime intravenously every 8 hours, up to a total maximum individual dose of 2 grams. With the exception of one study patient who received a single cefepime dose for surgical prophylaxis, the patients received cefepime for 2 to 13 days. Elimination half-life, steady-state distribution volume, total body clearance, and renal clearance after the first dose administration averaged 1.7 hours, 0.35 l/kg, and 3.1 ml/min/kg and 1.9 ml/min/kg, respectively. Although cefepime half-life and mean residence time, were slightly longer for subjects < 6 months of age than for older subjects, no differences in cefepime disposition characteristics between the first dose and steady-state evaluation were observed. The half-life (1.8 versus 1.9 hours), and the mean residence time (2.3 versus 3.2 hours), were slightly prolonged after intramuscular administration, reflecting the influenzae of absorption from the intramuscular injection site on cefepime elimination. Bioavailability after intramuscular administration averaged 82% (range, 61 to 124%). Fifty-seven percent of the first dose and 88.9% of the last dose were recovered as unchanged drug in urine over 8- and 24-hour sampling periods, respectively. These pharmacokinetic data support a single cefepime dosing strategy for patients ≥ 2 months of age. The integration of the cefepime pharmacokinetic data with MICs for important pathogens responsible for infections in infants and children supports the administration of a dose of 50 mg/kg cefepime every 12 hours for patients ≥ 2 months of age to treat infections caused by pathogens for which cefepime MICs are ≤ 8 µg/ml.

Table-1: Pharmacokinetic parameters of cefepime in neonates and children. The figures are the mean ± SD, if not otherwise stated.

Development stage	Number of cases	Clearance (ml/min/kg)	Distribution volume (l/kg)	Half-life (hours)	Trough concentration (µg/ml)	Peak concentration (µg/ml)	Reference
Preterm infants	32	1.03±0.40	0.40±1.0	5.09±1.80	30.56±19.52	190.02±31.25	25
Term infants	12	1.24±0.30	0.35±0.03	3.59±0.61	15.42±6.72	192.92±19.64	
31.7±2.7 GA (weeks)	31	1.20±0.49	0.41±0.12	4.32±1.8	18.39±13.3	120±38.5	26
30 .5+5.3 GA (weeks)	54	1.5±0.45	0.43±0.13	4.9±2.1	18±10 A	89+2.7 A	28
2.1 months to 16.4 years	31	2.8±1.4	0.33±0.1	1.8±0.6	6±7	I84.2±38	29
Adults	---	1.8 (1.7-2.5) B	0.26 (0.24-0.31)	2.1 (1.3-2.4) B	---	---	30 B

GA: Gestational age; A: estimated for 30 mg/kg every 12 hours; B: median (range) of reported clearance and half-life values from 16 single-dose studies, SD: Standard deviation.

4-DISCUSSION

Cefepime is a 4th generation cephalosporins with antimicrobial activity similar to 3rd generation cephalosporins. Potential advantages include: more rapid penetration through the cell wall of gram-negative pathogens; enhanced stability to hydrolysis by β-lactamases; and enhanced affinity for penicillin-binding proteins (1). Cefepime distributes widely in body tissues and fluids (i.e. cerebrospinal fluid, bile, bronchial secretions, ascitic fluid, and middle ear). Cefepime plasma protein binding is low (≤ 20%), and it is primarily excreted unchanged in the urine. Serum half-life in infants older than 2 months of age is approximately 2 hours (2). Cefepime is active against gram-negative microorganisms such as Escherichia coli, Haemophilus influenzae, Enterobacter, Klebsiella, Morganella, Neisseria, Serratia, and Proteus species, especially Pseudomonas aeruginosa that is resistant to 3rd generation cephalosporins. Cefepime is also active against serious infections caused by susceptible gram-positive microorganisms (e.g. Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, and Staphylococcus aureus) (2).

Cefepime possesses superior bactericidal action compared to other cephalosporins. Arnold et al. (6), compared the laboratory events in infants treated with cefepime or ceftazidime in the first 120 days of life. Laboratory adverse events occurred more frequently on days of therapy with ceftazidime than cefepime (373 versus 341 per 1,000 infant days, $P < 0.001$). Seizures were the most commonly observed clinical adverse event, occurring in 3% of ceftazidime-treated infants and 4% of cefepime-treated infants ($P = 0.52$). Mortality was similar between the ceftazidime and cefepime groups (5% versus 3%, respectively, $P = 0.07$).

Jones et al. (7), compared the antimicrobial potency of broad-spectrum parenteral cephalosporins. The microorganisms tested were Staphylococcus aureus, Moraxella catarralis, Coagulase-negative staphylococcus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella species, Enterococcus species, and β-hemolytic streptococci. Both cefepime and ceftriaxone had the highest bactericidal activity. Cefepime was also the most active β-lactam agent tested against Enterobacter species (MIC_{90}, 2 µg/ml; 99.3% susceptibility), whereas the susceptibility rates of other broad-spectrum β-lactams (ceftriaxone, ceftazidime and piperacillin-tazobactam), were significantly lower (78.4% to 81.5%). The present results indicate that cefepime was the most broad-spectrum cephalosporin analyzed and remains a very potent alternative for the treatment of contemporary pediatric infections. Saez-Llorens et al. (8), compared the treatment of bacterial meningitis with cefepime or cefotaxime in 90 infants and children. Six (7%) patients died two treated with cefepime and 4 treated with cefotaxime. Clinical response, cerebral fluid sterilization, development of complications, antibiotic toxicity, and hospital stay, were similar for the two treatment regimens.

Sarashina et al. (9), compared the efficacy and safety of cefepime and cefozopran empirical monotherapy in pediatric cancer patients with febrile neutropenia. Success was defined as resolution of febrile episodes and clinical signs of infection within 120 hours following the start of antibiotic therapy. The success rate was not significantly different between cefepime and cefozopran. Extended-infusion consists of administering cefepime intravenously for over 3 hours. Cefepime intravenous dose of 50 mg/kg over 30 min every 12 and 8 hours achieved probabilities of target attainment of only 15% and 79%, respectively, for Pseudomonas aeruginosa isolates (MICs 8

μg/ml) (11). However, when cefepime was administered over 3 hours, probabilities of target attainment increased to 57% and 100% with every 12- and 8-hour dosing, respectively, for Pseudomonas aeruginosa (11). The most active agents against Pseudomonas aeruginosa are amikacin, cefepime, ceftazidime, colistin, doripenem, meropenem and piperacillin-tazobactam, respectively, with MIC_{90}s (μg/ml) of 32, 16, 32, 2, 4, 8, and 64, respectively (15). Overall, the most active agents versus gram-positive cocci were vancomicin, linezolid, cefepime, doripenem, ertapenem, meropenem piperacillin-tazobactam, and tigecycline.

Sharma et al. (16), determined the causative bacteria and pattern of susceptibility to antibiotics in neonatal intensive care unit. The most common organism isolated was Staphylococcus aureus (37.22%) followed by Klebsiella pneumoniae (27.01%), and Escherichia coli (19.70%). The gram-positive organisms, except Streptococci, displayed a high degree of resistance to most penicillins and ciprofloxacin but were sensitive to vancomycin, amikacin, cefepime and ciprofloxacin amongst most gram-negative. Cefepime, amikacin and meropenem were effective in most cases.

Dzierzanowska-Fangrat et al. (17), determined the antimicrobial susceptibility of Enterobacteriacae to cefotaxime, ceftazidime and cefepime. They were 73%, 73%, and 87%, respectively. The susceptibility of Pseudomonas aeruginosa to both ceftazidime and cefepime was 76%. Bujdakova et al. (18), observed that Escherichia coli, Klebsiella species, Enterobacter species, Pantoea agglomerans, Citrobacter freundii and Serratia marcescens strains isolated from children between 0 and 3 years were resistant to ampicillin, cefoxitin, cefotaxime, ceftriaxone, and aztreonam, but were susceptible to cefepime and imipenem. The β-lactam resistance was due to production of β-lactamase and ceftazidime proved to be a stronger β-lactamase inductor than ceftriaxone.

Febrile neutropenia is associated with significant morbidity and mortality. Naseem et al. (19), checked the effectiveness of ticarcillin/clavulanate versus cefepime as monotherapy in febrile neutropenia in lymphoma infants, and also checked the tolerability profile of both drugs. The age of neonates ranged from 0 to 65 days. Cefepime was administered intravenously at the dose of 2 grams every 8 hours or ticarcillin/clavulanate at a dose of 3.2 grams every 6 hours for empirical monotherapy in febrile neutropenia. The overall response rate to therapy was compared in two groups on day 7 after start of therapy. Overall good response rate was statistically significant in two groups with 31% in cefepime and 51% in ticarcillin/clavulanate group ($P = 0.035$). On day 7 of therapy, the adverse effects were not different in the two groups. Use of cefepime in combination or alone in febrile neutropenia is approved by FDA. Cefepime seems to be more efficacious than ticarcillin/clavulanate and may be associated with lesser requirement of aminoglycoside, glycopeptides or both.

De Araujo et al. (20), verified if restriction of cefepime would ameliorate broad-spectrum susceptibility of gram-negative isolates. Cefepime has a greater propensity to select multiresistance gram-negative pathogens than piperacillin/tazobactam, and should not be used extensively in neonatal intensive care. The antibiotic resistance pattern was used to characterize the isolates, and a retrospective observational study was performed to assess the relationship between antimicrobial use and bacterial resistance (21). An Escherichia coli infection was diagnosed in 1.4% of 36,179 admitted to the hospital. Of the 519 isolates, 489 (94.2%) were resistant to at least one antibiotic. Twenty antibiotics were tested

and the percent of resistance ranged from 86% (ampicillin) and 10% (amikacin). The resistance to cefepime was 32%. The pattern of antibiotic resistance amongst gram-negative bacteria in pediatric units was studied prospectively over 6 months (22). A total of 109 patients admitted to intensive care and oncology units were tested. The commonest isolates were Klebsiella species (36.5%), and Pseudomonas aeruginosa (20.0%). The isolates showed lower susceptibility rates to the 3rd generation cephalosporins (47 to 62%), compared to cefepime (91%).

The rates of multidrug-resistant, extensively drug-resistant and pandrug-resistant isolates among non-fermenting gram-negative bacilli, particularly Pseudomonas aeruginosa, have risen worldwide. Dantas et al. (23), analyzed the first episodes of Pseudomonas aeruginosa bacteremia. Antimicrobial susceptibility testing was conducted; phenotypic detection of metallo-β-lactamase and PCR of metallo-β-lactamase genes, were performed on carbapenem-resistant strains. Amongst the 120 Pseudomonas aeruginosa isolates, 45.8% were resistant to carbapenem and 36 strains were tested for metallo-β-lactamase detection. A total of 30% were phenotypically positive and, of these, 77.8% expressed a metallo-β-lactamase gene, bla (SPM-1) (57%), and bla (VIM-type) (43%). The resistance rates to ceftazidime, cefepime, piperacillin/tazobactam, carbapenem, fluoroquinone, and aminoglycoside ranged from 35% and 55% and resistance rate to cefepime was 42%. Previous antibiotic use, length of a hospital stay $\geq$ 30 days prior Pseudomonas aeruginosa, and several medical and surgical procedures were common independent risk factors for antimicrobial resistance. Cefepime resistance, multi-drug resistance and extensive drug resistance were independently associated with inappropriate therapy, which was an important predictor of mortality, being-synergistic with the severity of the underlying disease. Salmonella species infections have been reported over recent years in hospitals in Argentina and other countries due to multiresistant strains. Jure et al. (24), characterized the extended-spectrum beta-lactamases in 3rd generation cephalosporin-resistant strains of Salmonella enterica serovar Oranienburg. The antibiotic susceptibility patterns of the isolates were analyzed and the beta-lactamases were characterized using phenotyping and genotyping methods. All the strains were resistant to ampicillin, cefotaxime, cefepime and aztreonam and partially susceptible to ceftazidime, thus corresponding well with the resistance phenotype conferred by CTX-M-type beta-lactamases. In neonates, the cefepime half-life ranges from 3.59$\pm$0.61 to 5.09$\pm$1.80 hours, and in children aged from 2.1 months to 16.4 years. In adults, the cefepime half-life ranges from 1.3 and 2.4 hours. In preterm infants, the half-life of cefepime is higher than in term infants (25). The primary route of cefepime elimination is from the kidneys, with over 80% of the drug recovered in the urine as unchanged drug in patients with normal renal function (1). Total cefepime clearance and renal clearance are similar to creatinine clearance, and glomerular filtration is thought to be the primary mechanism of renal excretion. The clearance of cefepime is similar in neonates and adults, whereas the cefepime distribution volume is larger in neonates than in adults. Trough concentrations of cefepime are double in preterm than term infants (25), and this finding may be explained by the longer half-life of cefepime in preterm than in term infants (25).

5- CONCLUSION

In conclusion, cefepime is approved in Europe and in the USA and the FDA approves cefepime in the treatment of

febrile neutropenia. Cefepime is a 4th generation cephalosporins with similar efficacy of third-generation cephalosporins. The advantages of cefepime are a more rapid penetration through the cell wall of gram-negative bacteria, enhanced stability to hydrolysis by β-lactamase, and enhanced affinity for penicillin-binding proteins. The primary route of cefepime elimination is from the kidney, with over 80% of the drug recovered in the urine as unchanged drug. Cefepime distributes widely in body tissues and fluids.

Cefepime is used in the treatment of serious infections caused by susceptible gram-negative bacteria such as Escherichia coli, Haemophilus influenzae, Enterobacter, Klebsiella, Morganella, Neisseria and Proteus species, and Pseudomonas aeruginosa that is resistant to third-generation cephalosporin. Cefepime is also active against serious infections caused by gram-positive bacteria such as Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, and Staphylococcus aureus. Cefepime has superior activity against nosocomial isolates of Enterobacter.

A 50 mg/kg cefepime administered as extended-infusion (3 hours), has higher target attainment than when administered over 30 min infusion. Cefepime is well-tolerated, but should be used judiciously as unnecessary, improper and prolonged use may lead to emergence of cefepime resistance.

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.

8- REFERENCES

1. Okamoto MP, Nakahiro RK, Chin A, Bedikian A. Cefepime clinical pharmacokinetics. Clin Pharmacokinet 1993; 25(2):88-102.

2. Young TE and Mangum B. NEOFAX. Twenty-third edition. Antimicrobials. 2010. Pp 24-25.

3. William A, Petri Jr. In the Goodman & Gilman's, the Pharmacological Basis of Therapeutics, 12th edition. Brunton L, Chabner B, Knollman B, eds. McGraw Hill: New York; 2011. Pp.1498-99.

4. Shahid SK. Cefepime and its role in pediatric infections. Recent Pat Antiinfect Drug Discov 2008; 3(2):145-8.

5. Hoffman JM, Frediani J, Herr M, Flynn PM, Adderson EE. The safety of cefepime and ceftazidime in pediatric oncology patients. Pediatr Blood Cancer 2013; 60(5):806-9.

6. Arnold CJ, Ericson J, Cho N, Tian J, Wilson S, Chu VH, et al. Best Pharmaceuticals for Children Act-Pediatric Trials Network Administrative Core Committee. Cefepime and Ceftazidime Safety in Hospitalized Infants. Pediatr Infect Dis J. 2015; 34(9):964-8.

7. Jones RN, Sader HS, Fritsche TR, Pottumarthy S. Comparisons of parenteral broad-spectrum cephalosporins tested against bacterial isolates from pediatric patients: report from the SENTRY Antimicrobial Surveillance Program (1998-2004). Diagn Microbiol Infect Dis. 2007; 57(1):109-16.

8. Sáez-Llorens X, Castaño E, García R, Báez C, Pérez M, Tejeira F, et al. Prospective randomized comparison of cefepime and cefotaxime for treatment of bacterial meningitis in infants and children. Antimicrob Agents Chemother 1995; 39(4):937-40.

9. Sarashina T, Kobayashi R, Yoshida M, Toriumi N, Suzuki D, Sano H, et al. A randomized trial of cefozopran versus cefepime as empirical antibiotic treatment of

febrile neutropenia in pediatric cancer patients. Pediatr Blood Cancer 2014; 61(11):1992-95.

10. Nichols KR, Karmire LC, Cox EG, Kays MB, Knoderer CA. Implementing extended-infusion cefepime as standard of care in a children's hospital: a prospective descriptive study. Ann Pharmacother 2015; 49(4):419-26.

11. Courter JD, Kuti JL, Girotto JE, Nicolau DP. Optimizing bactericidal exposure for beta-lactams using prolonged and continuous infusions in the pediatric population. Pediatr Blood Cancer 2009; 53(3):379-85.

12. Walker MC, Lam WM, Manasco KB. Continuous and extended infusions of β-lactam antibiotics in the pediatric population. Ann Pharmacother 2012; 46(11):1537-46.

13. Bauer KA, West JE, O'Brien JM, Goff DA. Extended-infusion cefepime reduces mortality in patients with Pseudomonas aeruginosa infections. Antimicrob Agents Chemother. 2013; 57(7):2907-12.

14. Nichols KR, Knoderer CA, Cox EG, Kays MB. System-wide implementation of the use of an extended-infusion piperacillin/tazobactam dosing strategy: feasibility of utilization from a children's hospital perspective. Clin Ther 2012; 34(6):1459-65.

15. Zhanel GG, Adam HJ, Low DE, Blondeau J, Decorby M, Karlowsky JA, et al. Canadian Antimicrobial Resistance Alliance (CARA). Antimicrobial susceptibility of 15,644 pathogens from Canadian hospitals: results of the CANWARD 2007-2009 study. Diagn Microbiol Infect Dis. 2011; 69(3):291-306.

16. Sharma CM, Agrawal RP, Sharan H, Kumar B, Sharma D, Bhatia SS. Neonatal Sepsis: Bacteria & their Susceptibility Pattern towards Antibiotics in Neonatal Intensive Care Unit. J Clin Diagn Res. 2013; 7(11):2511-13.

17. Dzierzanowska-Fangrat K, Semczuk K, Łopaciuk U, Kurlenda J, Małafiej E, Puacz E, et al. Antimicrobial susceptibility of aerobic microorganisms isolated from intraabdominal infections in pediatric patients in Poland. Med Sci Monit. 2005; 11(5):CR 241-5.

18. 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.

19. Naseem A, Hussain Y, Ahmad B, Aziz MT, Ahmad M, Hameed H. A prospective study of cefepime versus ticarcilline/clavulanate as empirical treatment of febrile neutropenia in lymphoma patients. J Pak Med Assoc. 2011; 61(1):18-22.

20. de Araujo OR, da Silva DC, Diegues AR, Arkader R, Cabral EA, Afonso MR, et al. Cefepime restriction improves gram-negative overall resistance patterns in neonatal intensive care unit. Braz J Infect Dis. 2007; 11(2):277-80.

21. Li JB, Yu YS, Ma YL, Zhou WL, Yu XZ. Prevalence and analysis of risk factors for infections caused by resistant Escherichia coli strains in Anhui, China. Infection 2001; 29(4):228-31.

22. Ariffin H, Navaratnam P, Kee TK, Balan G. Antibiotic resistance patterns in nosocomial gram-negative bacterial infections in units with heavy antibiotic usage. J Trop Pediatr 2004; 50(1):26-31.

23. Dantas RC, Ferreira ML, Gontijo-Filho PP, Ribas RM. Pseudomonas aeruginosa bacteraemia: independent risk factors for mortality and impact of resistance on outcome. J Med Microbiol 2014; 63(Pt 12):1679-87.

24. Jure MA, Aulet O, Trejo A, Castillo M. Extended-spectrum beta-lactamase-producing Salmonella enterica serovar Oranienburg (CTX-M-2 group) in a pediatric hospital in Tucumán, Argentina. Rev Soc Bras Med Trop. 2010; 43(2):121-4.

25. Shoji K, Bradley JS, Reed MD, van den Anker JN, Domonoske C, Capparelli EV. Population Pharmacokinetic Assessment and Pharmacodynamic Implications of Pediatric Cefepime Dosing for Susceptible-Dose-Dependent Organisms. Antimicrob Agents Chemother 2016; 60(4):2150-56.

26. Lima-Rogel V, Medina-Rojas EL, Del Carmen Milán-Segovia R, Noyola DE, Nieto-Aguirre K, López-Delarosa A, et al. Population pharmacokinetics of cefepime in neonates with severe nosocomial infections. J Clin Pharm Ther 2008;33(3):295-306.

27. Koren G. Therapeutic drug monitoring principles in the neonate. National Academy of CLinical Biochemistry. Clin Chem. 1997; 43(1):222-7.

28. Capparelli E, Hochwald C, Rasmussen M, Parham A, Bradley J, Moya F. Population pharmacokinetics of cefepime in the neonate. Antimicrob Agents Chemother 2005; 49(7):2760-66.

29. Reed MD, Yamashita TS, Knupp CK, Veazey JM Jr, Blumer JL. Pharmacokinetics of intravenously and intramuscularly administered cefepime in infants and children. Antimicrob Agents Chemother 1997; 41(8):1783-87.

30. Thummel KE, Shen DD, Isoherranen N. In the Goodman & Gilman's, the Pharmacological Basis of Therapeutics, 12th edition. Brunton L, Chabner B, Knollman B, eds. McGraw Hill: New York; 2011. Pp. 1911.