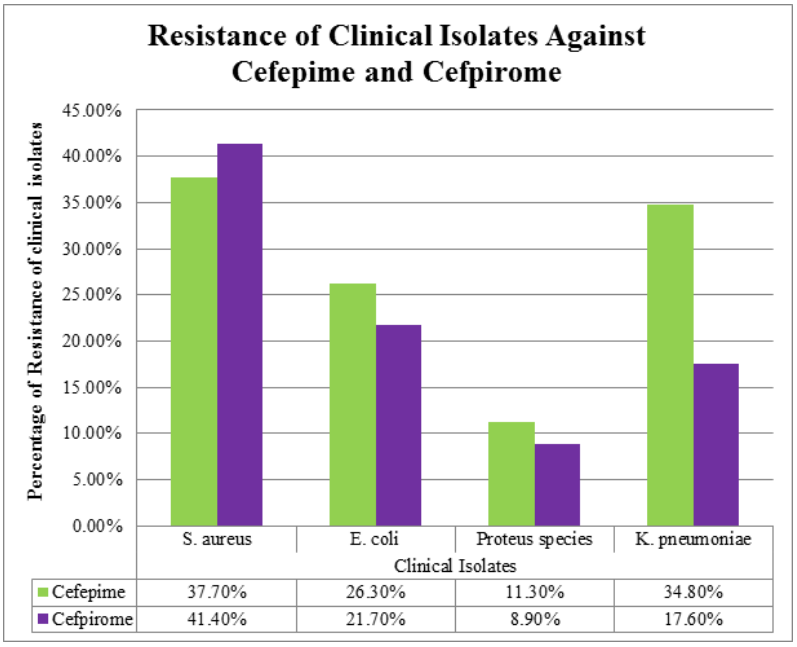
In vitro bactericidal activity of cefepime and cefpirome against clinical isolates at Karachi

Adeel Arsalan[1*], Syed Baqar Shayam Naqvi[2], Syed Abid Ali[3], Sadia Ahmed[1] and Osama Shakeel[4]

[1]Institute of Pharmaceutical Sciences, Baqai Medical University, Toll Plaza, Super Highway, Gadap Road, Karachi, Pakistan
[2]Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan
[3]H.E.J. Research Institute of Chemistry, ICCBS, University of Karachi, Karachi, Pakistan
[4]Karachi Medical and Dental College, Karachi, Pakistan

Graphical abstract



Abstract: Antibiotics not only support to alleviate the infections but also facilitate to avert the multiplication of microbes. Due to the irrational use of antibiotics, the resistance of antibiotics has been augmented which results may increase in morbidity and mortality with the span of time. World renowned regulatory bodies like Food and Drug Administration (FDA), Center of Disease Control and Prevention (CDC), and World Health Organization (WHO) vigorously advocate the surveillance of the resistance of antibiotics. During the present study by Kirby-Bauer disk diffusion method 141 clinical isolates of *Staphylococcus aureus* (n=47, 33.34%), *Escherichia coli* (n=54, 38.3%), *Proteus* species (n=26, 18.4%)**,** and *Klebsiella pneumoniae* (n=14, 9.92%) are evaluated against cefepime and cefpirome which comes of fourth generation cephalosporin. It has been found that cefpirome has better bactericidal activity than cefepime against *E. coli* and *K. pneumoniae* while cefepime has been possessed better antibacterial activity against *S. aureus* and *Proteus* species which were isolated from respiratory tract infections, blood stream infection, intra-abdominal and urinary tract infections, and skin and soft tissue infections. *K. pneumoniae*, *E. coli*, *Proteus* species, and *S. aureus* were 34.8%, 26.3%, 11.3%, and 37.7% resistance against cefepime respectively. *S. aureus*, *E. coli*, *K. pneumoniae*, *Proteus* species has shown 41.4%, 21.7%, 17.6%, and 8.9% resistance against cefpirome correspondingly.

Keywords: Cefepime, cefpirome, clinical isolates, *in-vitro,* susceptibility.

INTRODUCTION

Cephalosporins are belonging to beta-lactam antibiotics with 6-membered dihydrothiazine ring, thus forming the cephem nuclei. Cephalosporins have superior efficacy with tolerability as compared to other group of antibiotics. Persons are less hypersensitive with cephalosporins as compared to other beta-lactams like penicillin and its derivates. Cephalosporins are generally classified into four generations (Harrison and Denise, 2008). Two new fifth generation cephalosporin ceftaroline (PPI 0903, formerly TAK-599), and ceftobiprole (BAL 9141) is

**Corresponding author:* e-mail: adeelarsalan@hotmail.com

under-trial with extended-spectrum cephalosporin activity against clinically important Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and *Enterococcus faecalis* (Noel *et al*., 2008; Saravolatz *et al*., 2011).

Bactericidal activity of antibiotics is mainly depends upon the concentration of drug in plasma and tissue. Microbes modify their traits to the antibiotics and convey their resistance qualities to their descendents (Craig, 1998). The resistance traits are developed due to suboptimal, irrational and extensive use (Knox *et al*., 2003), low dose antibiotics (Craig, 1998), long course of antibiotics (Sae-Tia and Chongsomchai, 2006), too early and too late administration (Sadique *et al*., 2009). It has been suggested by many workers that low concentration of antibiotics is one of the influential factor to enhance the resistance (Fantin *et al*., 1994; Mouton and den Hollander, 1994; Davies *et al*., 2000). The dosing interval for beta-lactams have been re-evaluated to keep plasma levels above distinct thresholds for prolong period of time (Crokaert, 2001). Moreover, since last two decades the use of broad spectrum antibiotics has been increased due to many factors like reduced drug expenditures, decreased drug interactions and risk for toxicity and other pharmacoeconomic benefits (Isais-Agdeppa and Bravo, 2005).

Due to good antibacterial activity even against resistant pathogens, mainly fourth generation zwitterionic cephalosporin, cefepime and cefpirome is indicated as empirical monotherapy for complicated urinary tract infections (UTIs), pneumonia, skin and soft tissue infections, intra-abdominal infections and febrile neutropenia **(**Endimiani *et al*., 2008).

Cefepime and cefpirome, fourth generation cephalosporins with certain benefits over the third generation cephalosporins and other penicillin derivatives like more resistant against beta-lactamase, extended spectrum of activity that includes many Gram-positive and Gram-negative bacteria, activity against multi-resistant bacteria and induction high potency, rapid penetration into the periplasmic space (Wynd and Paladino, 1996). Cefepime and cefpirome are the drugs of choice in life threatening nosocomial infections, febrile neutropenia, septicemia, and serious infections in patients of intensive care units (ICU) due to its high resistance against beta-lactamases. Cefepime and cefpirome have been described in some reports as less prone than other cephalosporins to hydrolysis by ESBLs as produced by Gram-negative pathogens (Wiseman and Lamb 1997; Angelescu and Apostol 2001). Cefepime and cefpirome have come of fourth generation of cephalosporin. Both antibiotics have not only broad spectrum activity but also possess bactericidal activity against resistant Gram-positive pathogens like MRSA, PRSP, *Streptococcus pyogenes* and extended-spectrum β-lactamases (ESBLs), producing Gram-negative *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia*, *Citrobacter*, *Proteus mirabilis* and less active against *Bacillus fragillis*. *Pseudomonas aeruginosa* has been mediated by the combination of hyper-production of class C chromosomal enzymes (i.e., AmpC) and/or upregulation of efflux pumps (Wynd and Paladino, 1996; Angelescu and Apostol 2001). The pharmacokinetic profile of cefepime and cefpirome has been shown in table 1.

The most common adverse effects associated with these two cephalosporins are same like rash and diarrhea, pruritus, urticaria, nausea, vomiting oral candidiasis, colitis, headache, fever, erythema and vaginitis (Sagawa *et al*., 2000; Chapman and Perry, 2003). Moreover, elevated liver function, blood urea nitrogen, or partial thromboplastin and prothrombin times has also been observed. Similar to any parenteral beta-lactam drug, transient neutropenia or thrombocytopenia may also be occurred with cefepime (Wynd and Paladino, 1996).

In low socioeconomic countries like Pakistan, around 80% of population has not been facilitated to avail antibiotic susceptibility test. The physicians have been usually prescribed more than one antibiotic, leading cause of antibiotic resistance (Ullah *et al*., 2009).

MATERIALS AND METHODS

Collection of specimens

One hundred and eighty nine clinical isolates belonging to different genera like *Staphylococcus aureus, Escherichia coli, and Proteus* and *Klebsiella* species were collected on sterile swabs from different patients as shown in table 2 and different tertiary care hospitals and pathological laboratories at Karachi from May 2012 to March 2013. The isolates were identified based on their colony characteristics on different media and confirmed by biochemical reactions. The isolates were inoculated in caso agar/ tryptic soya agar slants. These slants had been preserved at 4^{o}C in the refrigerator. Antimicrobial resistance (AMR) has been determined by Clinical and Laboratory Standard Institute (CLSI, formally NCCLS) reference disk diffusion (Kirby-Bauer) method (Bauer *et al*., 1966; CLSI, 2011).

Preparation of inoculums

Muller-Hilton Broth (MHB) was used to prepare inoculums and matched with McFarland standard. All tubes were incubated at 37^{o}C for few hours to develop the required turbidity as that of the McFarland standard. Muller- Hilton Agar (MHA) was used to determine the sensitivity of clinical isolates. Bauer, Kirby, Sherris and Tuck strongly suggested MHA for performing antibiotic

susceptibility tests using a single disk of high concentration (Bauer *et al*., 1966). This unsupplemented medium has been preferred by the Clinical and Laboratory Standard Institute for various reasons (CLSI, 2011).

Inoculation of bacterial culture

A sterile swab was dipped into a broth suspension of bacterial culture. Excess inoculum was removed by rotating the swab against the inside wall of the tube with slim pressure. The whole surface of MHA plate was then streaked uniformly in three directions approximately at 60^{o} angle from each other. The lid was then replaced and the plates were allowed to dry for 10-15 min.

Placement of antibiotic disc

The appropriate antibiotic impregnated discs were placed on the agar surface with sterile forceps. Each disc was pressed down gently with the forcep to assure good contact with agar surface. The disc should be distributed such that each is at least 24 mm from center to center of its nearer neighbor and 12 mm from the edge of plate.

Incubation

The plates were overturned within 15 min of placing the disc on agar and incubated at 35-37^{o}C for 24 hours. After incubation the diameter of the clear zones around the antibiotic disc were measured by using vernier caliper. All the bench work was carried out near a flame to create a zone of inhibition of invading bacteria and maintained the integrity.

RESULTS

In the present study, cefepime and cefpirome are belonging to fourth generation cephalosporin. These fourth generation cephalosporins were evaluated against the most common pathogens isolated in infections like *S. aureus, E. coli,* and *K. pneumoniae, Proteus* species. These clinical isolates has been mainly involved in various infections like respiratory tract infections, blood stream infection, intra-abdominal and urinary tract infections, burn infections, wound infection and surgical site infections (Wiseman and Lamb, 1997; Angelescu and Apostol *et al*., 2001; Witte *et al*., 2008).

One hundred and forty one clinical isolates were collected from different clinical laboratories of tertiary care hospitals at Karachi. Among these clinical isolates mostly *Escherichia coli* (38.3%) was collected, secondly its contender was *Staphylococcus aureus* (33.34%) while *Proteus* species (18.4%), and *Klebsiella pneumoniae* (9.92%) were also isolated.

The outcome susceptibility of clinical isolates has been shown in table 3 and graphical figure. Both cefepime and cefpirome discs contain 30µg content. By the present study, it has been found that *E. coli* and *K. pneumoniae* and *Proteus* species were more susceptible against cefpirome while cefepime has shown better bactericidal activity against *S. aureus*. *S. aureus*, *K. pneumoniae, E. coli*, and *Proteus* species were 37.7%, 34.8%, 26.3% and 11.3% resistance against cefepime respectively. *S. aureus*, *E. coli*, *K. pneumoniae*, *Proteus* species were 41.4%, 21.7%, 17.6%, and 8.9% resistant against cefpirome.

DISCUSSION

In vitro bactericidal action has been commonly performed, because provide an idea of resistance of antibiotics against pathogens inside the body (Jones and Preston, 1983). Bacteria has been transferred their resistant traits to their new generations, which is not a hidden iceberg for health-associated professional but also for the pharmaceutical companies. Microorganisms are present everywhere either in soil, water, food, air and even in and on human (Chong *et al.*, 2010; Arsalan *et al.*, 2010; Arsalan *et al.*, 2013a; Arsalan *et al.*, 2013b; Arsalan *et al.*, 2013c). The unreasonable use of antibiotics has been one of the major factor, amplified the probability of resistance in human beings (Arsalan *et al*., 2014).

Cephalosporins, belonging to β-lactam antibiotics, are one of the most frequently prescribed antibiotics. Still four generation of cephalosporins are marketed by pharmaceutical companies in Pakistan. Due to its better tolerability, durability, and excellent pharmacokinetic profile, it is one of the most trusted class of antibiotics. Several pathogens have been produced Extended-Spectrum Beta-Lactamase (ESBL) enzyme which aid in the resistance against bactericidal activity of cephalosporins. Ceftaroline and ceftobiprole are the novel broad spectrum cephalosporins, have been soon introduced in market due to the trustworthy profile of cephalosporins (Lemaire *et al*., 2009; Biek *et al*., 2010).

Due to illogical use of antibiotics, resistance has been increased. Microorganisms have been transferred their resistance traits to their next generation. Globally, it has been observed that Gram-positive are the main concerned in infections, the infections caused by pathogens can also be reduced by preventive measurements (Arsalan *et al.*, 2010, Arsalan *et al.*, 2014). It has been noted 60-70% reported infections have been related to Gram-positive. However, Gram-negative pathogens prominently *E. coli* and *K. pneumoniae* and *Proteus* species have been caused several life threatening infections (Isais-Agdeppa and Bravo, 2005). Antibiotics resistance of pathogens has been increased by long-term care, and hospital settings, which has been possessed severe problem in the choice of an appropriate antibiotic for proper treatment (Witte *et al*., 2008; Gaynes and Edwards 2005).

Table 1: Pharmacokinetic Profile of Cefepime and Cefpirome

Drug	Half-Life	Steady State C_{max}	Volume of Distribution	Serum Protein Binding	Mean Renal Clearance (ClR)
Cefepime	1.3 to 1.9 hours (Blumer *et al*., 2001)	50-mg/kg intravenous regimen was 177 mg/l for every 12 h and 188 mg/l for every 8 h. (Blumer *et al*., 2001)	18.0 ± 2.0l (Blumer *et al*., 2001)	Approx. 20% (Barbhaiya *et al*., 1992)	105 ml/ min (Barbhaiya *et al*., 1992) 85% excreted unchanged in urine (Wynd and Paladino, 1996)
Cefpirome	1.7 to 2.3 hours (dexa medica, 2013)	Value of C_{max} between 86.7 and 97.4 mg / L after administration of a single IV injection at a dose of cefpirome 1 g and between 23.2 and 30.6 mg / L 2 hours after administration of IM with the same doses (cefpirome 1 g) (dexa medica, 2013)	Volume of distribution at steady state is between 15.3 and 21.3 L (dexa medica, 2013)	Approx. 8-12% (dexa medica, 2013)	Total renal clearance is approximately 6.6 to 10.6 liters / h and renal clearance rate ranged from 4.9 to 6.7 liters / hour (dexa medica, 2013)

Table 2: Summary of clinical isolates

Clinical Isolates	Source of isolates	Number of isolates
Staphylococcus aureus	Surgical, burn and accidental wound pus (skin and soft tissue infections), blood (blood stream infection), sputum (respiratory tract infections)	47
Escherichia coli	Stool and urine (intra-abdominal and urinary tract infections), blood (blood stream infection), surgical, burn and accidental wound pus (skin and soft tissue infections)	54
Proteus species	Wounds and urine (urinary tract and skin and soft tissue infections)	26
Klebsiella pneumoniae	Sputum (respiratory tract infections), blood (blood stream infection)	14

Table 3: Resistance Pattern of Clinical Isolates Involved in Different Infections

Antibiotics	Clinical Isolates			
	Staphylococcus aureus	*Escherichia coli*	*Proteus* species	*Klebsiella pneumoniae*
Cefepime	37.7%	26.3%	11.3%	34.8%
Cefpirome	41.4%	21.7%	8.9%	17.6%

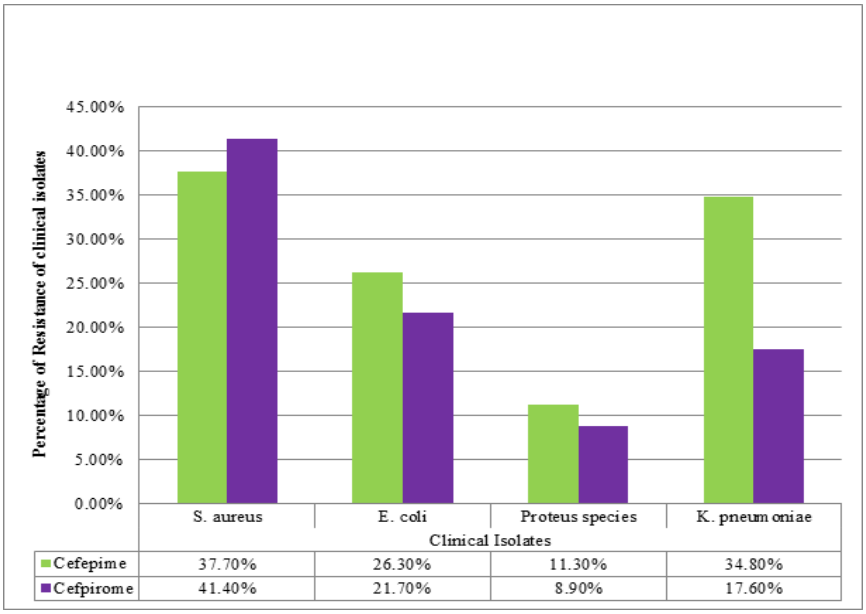


Fig. 1: Resistance Pattern of Clinical isolates against Cefepime and Cefpirome

S. aureus is one of the most frequent reported clinical isolate in present study. Mainly, infections are associated with Gram-positive pathogens alone or in mixed culture of Gram-negative and Gram-positive bacteria. *S. aureus* has been commonly isolated from surgical, nosocomial, burn, and blood stream infections (Yoshikawa and Bradley 2002; Zorgani *et al.,* 2010). It has been found that *S. aureus* is most resistant against cefepime and cefpirome among all clinical isolates. The present study has shown 37.7% resistant to cefepime. Nasiri *et al*. (2013) supported the present study by 30% *S. aureus* resistance against cefepime. However, 41.4% *S. aureus* were resistant to cefpirome in current study. Chaudhury *et al.* (2003) have been observed 56.8% resistance of *S. aureus* against cefpirome. In contrast, of present study 20.4% bacteriacidal activity of *S. aureus* has been reported in Mexico (Santos *et al.,* 2000).

E. coli is one the most frequent isolated pathogen in intra-abdominal and urinary tract infections (Sader *et al*., 2001). The present study revealed 26.3% *E. coli* resistance against cefepime supported by Liao and co-workers found 23% resistance (Liao *et al*., 2006). Moreover, 21.7% *E. coli* was resistance against cefpirome in present study. *E. coli* against cefpirome has shown 13% and 33.4% resistance by Hafeez and co-workers (2000) and Gupta *et al.* (2006) respectively.

Klebsiella pneumoniae has been involved in respiratory tract infections, blood stream infection, and urinary tract infections. *K. pneumoniae* is difficult to treat because fewer antibiotics are effective against *K. pneumoniae.* The outcome of current study has shown 34.8% and 17.6% *K. pneumoniae* resistance against cefepime and cefpirome respectively. Bedenic and co-workers (2001) have found 23.8% *K. pneumoniae* resistance against cefpirome. 84% susceptibility has been reported by Hafeez *et al.* (2000). Moreover, 73.4% and 64.7% susceptibility of *K. pneumoniae* against cefepime has been reported by Liao and mates (2006) and da Silva Nogueira *et al.* (2011) correspondingly.

Proteus species have been ubiquitously found. It is present in intravenous solutions, on the skin of human-being food, and in contaminated water. *Proteus* species were resistant to in general by used antibiotics leading to a higher prevalence of resistant bacteria (Feglo *et al.*, 2010). In present study, *Proteus* species have been shown 11.3% and 8.9% resistance against cefipime and cefpirome respectively. There is huge diversity in the result of *Proteus* species susceptibility against cefpirome, Gupta and his co-workers (2006) has shown 100% sensitivity, similarly, 97% and 85% antibacterial activity of cefpirom against *Proteus* species by Hafeez and colleagues (2000) and Sader *et al*. (2005) respectively.

It has been concluded from the present study that cefpirome has been possessed better susceptibility against *E. coli, K. pneumoniae* and *Proteus* species, while cefipime has shown better antibacterial activity against *S. aureus.*

CONCLUSION

Resistance of antibiotics is now become curse to humankind. Globally prominent regulatory authorities like FDA, infection prevention society (IPS), CDC, WHO and local bodies in even local bodies for prevention of infection. In Pakistan, like Infection Control Society of Pakistan (ICSP) and Infectious Disease Society of Pakistan (IDSP) has been strongly discouraged the unjustified use of antibiotics in Pakistan. For irrational use of antibiotics, awareness program should be initiated. Health associated professionals should always try to check the *in-vitro* susceptibility of pathogens for proper treatment. In the mean while, it should be preferred to use the empirical therapy for infection control and preventions. The present study has been strongly recommended to prepare local guidelines at least for empirical therapy for the use of antibiotics in particular infections.

ACKNOWLEDGEMENT

We would like to thank Prof. Dr. Iqbal Ahmad for his keen interest and valuable suggestions during the preparation of manuscript.

REFERENCES

Angelescu M and Apostol A (2001). Cefepime (maxipime), large spectrum 4th generation cephalosporin, resistant to beta-lactamases. *Chirurgia. (Bucur)*, **96**: 547-552.

Arsalan A, Sabah A, Ahmad I, Naqvi SBS, Ali SI (2010). The role of antiseptic in surgery. *J. Baqai Med Univ.*, **13**(2): 47-54.

Arsalan A, Anwar Z, Ahmed I, Saba A and Naqvi SBS (2013a). Microbes in pediatric infant formula. *Annals. Food Sci. Technol.*, **14**(1): 90-99.

Arsalan A, Anwar Z, Ahmad I, Shad Z and Ahmed S (2013b). *Cronobacter sakazakii:* An emerging contaminant in Pediatric infant milk formula. *Int. Res. J. Pharm*., **4**(4):17-22.

Arsalan A, Naqvi SBS, Ali SI and Anwar Z (2013c). Contamination of microorganisms in pediatric infant formula. *Annal. Food Sci. Technol.*, **14**(2): 318-326.

Arsalan A, Naqvi SBS, Sabah A, Bano R and Ali SI (2014). Resistance pattern of clinical isolates involved in surgical site infections. *Pak. J. Pharm. Sci.*, **27**(1): 97-102.

Barbhaiya RH, Forgue ST, Gleason CR, Knupp CA, Pittman KA, Weidler DJ, Movahhed H, Tenney J and Martin RR (1992). Pharmacokinetics of cefepime after single and multiple intravenous administrations in

healthy subjects. *Antimicrob. Agents Chemother*., **36**(3): 552-557.

Bauer AL, Kirby WMM, Sherris JC and Turck M (1966). Antibiotic susceptibility testing by a standardized single disk method. *Am. J. Clin. Pathol.,* **45**: 493-496.

Bedenic B, Beader N and Zagar Z (2001). Effect of inoculum size on the anti-bacterial activity of cefpirome and cefepime against Klebsiella pneumoniae strains producing SHV extended-spectrum beta-lactamases. *Clin. Microbiol. Infect*., **7**(11): 626-635.

Biek D, Critchley IA, Riccobene TA and Dirk A Thye DA (2010). Ceftaroline fosamil: A novel broad-spectrum cephalosporin with expanded anti-Gram-positive activity. *J. Antimicrob. Chemother*., **65**(4): 9-16.

Blumer JL, Reed MD and Knupp C (2001). Review of the pharmacokinetics of cefepime in children. *Pediatr. Infect. Dis. J*., **20**(3): 337-342.

Chapman TM and Perry CM (2003). Cefepime: A review of its use in the management of hospitalized patients with pneumonia. *Am. J. Respir. Med.*, **2**: 75-107.

Chaudhury A. *In vitro* activity of cefpirome: A new fourth generation cephalosporin. *Ind. J. Med. Microbiol.*, **21**(1): 52-55.

Chong MN, Jin B, Chow CWK and Saint C (2010). Recent developments in photocatalytic water treatment technology: A review. *Water Res.*, **44**(10): 2997-3027.

Clinical and Laboratory Standards Institute (2011). Performance standards for antimicrobial disk susceptibility tests, Twenty-First International Supplement. M100-S21, CLSI, Wayne, PA, USA, pp.42-44, 68-72.

Craig WA (1998). Pharmacokinetic/pharmacodynamic parameters: Rationale for anti-bacterial dosing of mice and men. *Clin. Infect. Dis*., **26**: 1-12.

Crokaert F (2001). Pharmacodynamics, a tool for a better use of antibiotics. *Intensive Care Med.*, **27**: 340-343.

da Silva Nogueira K, Daur AV, de Messias Reason IT Ana Cristina Gales AC and Costa LMD (2011). Cefepime versus extended spectrum β-lactamase-producing Enterobacteriaceae. *Braz. J. Infect. Dis.,* **15**(2): 167-169.

Davies J, Wendon J, Wyncoll D and Wade J (2000). Antibiotic infusions reduce the incidence of resistant organisms in liver intensive care (abstract). *Intensive Care Med.*, **26**: 269.

DEXA MEDICA http://www.dexa-medica.com/ourproducts/prescriptionproducts/detail.php?id=15&idc=9 (Accessed on July 03, 2013)

Endimiani A, Perez F and Bonomo RA (2008). Cefepime: A reappraisal in an era of increasing anti-microbial resistance. *Expert Rev. Anti. Infect. Ther.*, **6**(6): 805-824.

Fantin B, Farinotti R, Thabaut A and Carbon C (1994). Conditions for the emergence of resistance to cefpirome and ceftazidime in experimental endocarditis due to *Pseudomonas aeruginosa*. *J. Antimicrob. Chemother.*, **33**: 563-569.

Feglo PK, Gbedema SY, Quay SNA, Adu-Sarkodie Y and Opoku-Okrah C (2010). Occurrence, species distribution and antibiotic resistance of Proteus isolates: A case study at the komfo anokye teaching hospital (KATH) in Ghana. *Int. J. Pharma Sci. Res.*, **1**(9): 347-352.

Gaynes R and Edwards JR (2005). Overview of nosocomial infections caused by Gram negative bacilli. *Clin. Infect. Dis.*, **41**(6): 848-854.

Gupta V, Datta P, Agnihotri N and Chander J (2006). Comparative *in vitro* activities of seven new beta-lactams, alone and in combination with beta-lactamase inhibitors, against clinical isolates resistant to third generation cephalosporins. *Braz. J. Infect. Dis.,* **10**(1): 22-25.

Hafeez S, Izhar M, Ahmed A, Afia Zafar A and Naeem M (2000). *In vitro* Anti-microbial activity of Cefpirome: A new fourth-generation Cephalosporin against clinically significant Bacteria. *J. Pak. Med. Assoc.*, **50**(8): 250-252.

Harrison CJ and Denise Bratcher D (2008). Cephalosporins: A Review. *Pediatric. Rev.*, **29**(8): 264-272.

Isais-Agdeppa AT and Bravo L (2005). A five-year retrospective study on the common microbial isolates and sensitivity pattern on blood culture of pediatric cancer patients admitted at the philippine general hospital for febrile neutropenia. *PIDSP Journal*, **9**(2): 19-24.

Jones RN and Preston DA (1983). The anti-microbial activity of cephalexin against old and new pathogens. *Postgrad. Med. J.*, **59**(5): 9-15.

Knox K, Lawsony W, Deanyz B and Holmesx A (2003). Multidisciplinary anti-microbial management and the role of the infectious diseases pharmacist: A UK perspective. *J. Hosp. Infect.*, **53**: 85-90

Lemaire S, Glupczynski Y, Duval V, Bernard Joris B, Paul M. Tulkens PM and Van Bambeke F (2009). Activities of ceftobiprole and other cephalosporins against extra cellular and intracellular (THP-1 Macrophages and Keratinocytes) Forms of methicillin-susceptible and methicillin resistant staphylococcus aureus. *Anti-microb. Ag. Chemother.*, **53**(6): 2289-2297.

Liao CH, Sheng WH, Wang JT Sun HY, Wang HK, Hsueh PR, Chen YC and Chang SC (2006). *In vitro* activities of 16 anti-microbial agents against clinical isolates of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* pneumoniae in two regional hospitals in Taiwan. *J. Microbiol. Immunol. Infect.*, **39**: 59-66.

Mouton JW and den Hollander JG (1994). Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an *in vitro* pharmacokinetic model. *Antimicrob. Agents Chemother.*, **38**: 931-936.

Nasiri MI, Naqvi SB, Zaidi AA, Saeed R and Raza G (2013). Report-comparative study on resistant pattern of clinical isolates against levofloxacin and cefepime. *Pak. J. Pharm. Sci.*, **26**(2): 415-419.

Noel GJ, Bush K, Bagchi P, Ianus J and Strauss RS (2008). A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. *Clin. Infect. Dis.,* **46**: 647-655.

Sader HS, Gales AC, Pfaller MA, Mendes RE, Zoccoli C, Barth A and Jones RN (2001). Pathogen frequency and resistance patterns in brazilian hospitals: Summary of results from Three Years of the Sentry Anti-microbial Surveillance Program. *Braz. J. Infect. Dis.,* **5**(4): 200-214.

Sadique I, Abid S, Aleem S, Anwar S, Hafeez M, Pasha MI and Butt F (2009). Single dose prophylaxis in obstetrics and gynaecological surgeries. *Annals*, **15**(4): 176-179.

Sae-Tia L and Chongsomchai C (2006). Appropriateness of anti-biotic prophylaxis in gynecologic surgery at Srina-garind Hospital. *J. Med. Assoc. Thai*., **89**: 2010-2014.

Sagawa T, Fuiuno T, Sakuragi N, Kishida T, Yamada H and Fuiimoto S (2000). Clinical study of cefpirome sulphate in obstetric and gynaecological infections. *J. Int. Med. Res.*, **28**(6): 288-99.

Santos JI, Arredondo JL and Vazquez V (2000). Bacterial isolates from hematology, oncology and intensive care units: Susceptibility to cefpirome and other beta-lactam antibiotics in a multicenter study in Mexico. *Curr. Ther. Res.*, **61**(5): 266-276.

Saravolatz LD, Stein GE and Johnson LB (2011). Ceftaroline: A novel cephalosporin with activity against Methicillin-resistant staphylococcus aureus. *Clin. Infect. Dis.*, **52**(9):1156-1163.

Ullah F, Malik SA and Ahmed J (2009). Anti-microbial susceptibility pattern and ESBL prevalence in *Klebsiella pneumoniae* from urinary tract infections in the North-West of Pakistan. *Afr. J. Microbiol. Res.*, **3**(11): 676-680.

Wiseman LR and Lamb HM (1997). Cefpirome: A review of its antibacterial activity, pharmacokinetic properties and clinical efficacy in the treatment of severe nosocomial infections and febrile neutropenia. *Drugs*, **54**: 117-140.

Witte W, Cuny C, Klare I, Nubel U, Strommenger B and Werner G (2008). Emergence and spread of antibiotic-resistant Gram-positive bacterial pathogens. *Int. J. Med. Microbiol.*, **298**(56): 365-77.

Wynd MA and Paladino JA (1996). Cefepime: A fourth-generation parenteral cephalosporin. *Ann. Pharmacother.*, **30**(12): 1414-1424.

Yoshikawa TT and Bradley SF (2002). *Staphylococcus aureus* Infections and Anti-biotic resistance in older Adults. *Clin. Infect. Dis.*, **34**(2): 211-216.

Zorgani A, Franka RA, Zaidi MM, Alshweref UM and Elgmati M (2010). Trends in nosocomial bloodstream infections in a burn intensive care unit: An eight-year survey. *Ann. Burns Fire Disasters*, **23**(2): 88-94.