Comparative Study on Resistance Pattern of Different Pathogens Against Cefixime and Cefepime

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ABSTRACT

Irrational use of antibiotics has fueled a major increase in prevalence of multi drug resistant pathogens, leading some to speculate that we are nearing the end of antibiotic era. The assessment of the activity of an antibiotic is crucial to the successful outcome of antimicrobial therapy. The objective of the study is to evaluate the resistance pattern between cefixime (a third generation cephalosporin) of 5µg and cefepime (a fourth generation cephalosporin) of 30µg, on a total of 138 different clinical isolates namely as; *Escherichia coli* (30%), *Staphylococcus aureus* (30%), *Salmonella typhi* (14%), *Klebsiella pneumoniae* (13%) and *Pseudomonas aeruginosa* (13%). The isolates were collected over a period of one year (January 2008 to January 2009) from pathological laboratories of different hospitals in Karachi, Pakistan, which comprised of 59 urine, 30 skin pus, 29 ear pus, 15 blood and 5 stool samples. In-vitro antibiotic sensitivity was performed by disk diffusion or Bauer-Kirby method using 0.5 McFarland standard. Cefepime showed good sensitivity of about 92.6% against *Escherichia coli,* 85% against *Staphylococcus aureus*, 94% against *Klebsiella pneumoniae*, 77.77% against *Pseudomonas aeruginosa* and 65% against *Salmonella typhi*. Cefixime showed least sensitivity against *Pseudomonas aeruginosa* (16.66%) and maximum effectiveness against *Salmonella typhi* (90%). Results of the study indicate that cefepime is more effective for the treatment of infections caused by the above pathogens except for *Salmonella typhi*. It is concluded that in the face of continuing development of resistance, considerable effort will be required to maintain the effectiveness of these drug groups.

Keywords: Cefixime, Cefepime, Disk Diffusion Method, Microbial Resistance, Pathogens.

INTRODUCTION

The early treatment failures with antibiotics did not represent a significant problem since other antimicrobial classes were available. It is the emergence of multiple resistances that is causing major problems in the clinic today (1). Different microbial species and stains have different degree of susceptibility to different chemotherapeutic agents. The susceptibility can change with time, even during therapy with a specific drug, thus the physician must know the sensitiveness of the pathogen before treatment can be started (2). Surveys of antibiotic use, have demonstrated that more than 50% of antibiotic prescribing can be inappropriate; in situations where they are either ineffective (viral infections) or the selected agent, dose and duration of use are inappropriate (3).

A number of effective antimicrobial agents such as, β-lactams, aminoglycosides, fluroquinolines, tetracyclines, and trimethoprim/sulfamethaxazole are available. But cephalosporins are currently among the most widely prescribed class of antibiotics in hospitals The number of 2nd, 3rd and even 4th generation cephalosporins has proliferated in recent years, there are now more than 30

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versions. Each generation has a broader spectrum of activity than the previous one (2, 4). Because of similarities in their beta-lactam ring structures, cross-react with penicillins and therefore should not be given to patients known to be penicillin allergic. Despite the fact, a patient allergic to penicillin has only about a 10% chance of being hypersensitive to cephalosporins also (5).

Cefixime is a semi synthetic, broad spectrum, third generation cephalosporin, similar to penicillins chemically in mechanism of action and toxicity but more stable than penicillins to many bacterial beta-lactamases. In vitro tests and clinical trials have indicated that most strains of the following organisms can be effectively eradicated by using adequate doses of cefixime .*Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae* (beta-lactamase positive and negative), *Moraxella catarrhalis* (formerly Branhamella catarrhalis), *Escherichia coli, Proteus mirabilis, and Neisseria gonorrheae* (beta-lactamase positive and negative) (6). It is administered orally in children and adults, once or twice daily with good antimicrobial activity against *Salmonella typhi.* Due the emergence of MDR *S. typhi* in endemic countries, alternative drugs for the treatment of typhoid fever are required. Santillán *et al*., in 2000 conducted a study to assess the efficacy of cefixime in the treatment of typhoid fever, and observed all strains included in the experiment were sensitive to cefixime (7). Cefixime is a safe, effective, and cheaper oral option for the treatment of multidrug-resistant enteric fever (8).

Cefepime is a 4th generation, broad-spectrum cephalosporin, with a higher degree of activity against both Gram-positive and Gram-negative bacteria. Cefepime is currently widely used in hospitals, for its approved indications, including empirical monotherapy for febrile neutropenia, pneumonia, bacteraemia, and urinary tract, abdominal, and skin or soft-tissue infections (9). Cefepime's superior activity is attributed to more rapid penetration into bacteria, the targeting of multiple penicillin-binding proteins, or lower affinity for several β-lactamases (10, 11). It possesses good activity against pathogens including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus aureus*, *Escherichia coli* and multiple drug resistant *Streptococcus pneumoniae, Enterobacter sp.* It is administered either intravenously or intramuscularly and exhibits linear pharmacokinetics. The drug is distributed widely, and 20% is protein bound. The elimination half-life in adults is approximately 2 hours, and in children, it is slightly less (1.7 hours) (12, 13). It represents an important therapeutic option for the empiric treatment of bacterial meningitis in children, based on the good clinical response and bacteriologic eradication rates (14).

The aim of study is to assess in vitro susceptibility of different microorganisms against these two broad spectrum cephalosporins (cefixime and cefepime) in local population of Karachi, Pakistan**,** using disk diffusion method for surveillance of emerging antimicrobial resistance.

MATERIAL AND METHODS:

Collection of Clinical Isolates

A total of 138 different clinical isolates including both Gram –ve and Gram +ve pathogens were collected over a period of one year (January 2008 to January 2009) from different pathological laboratories (Ehsanullah laboratory, Laboratory of Liaquat College of medicine and dentistry and Dar-ul- Sehat hospital and Agha khan university hospital) located in Karachi, Pakistan. These pathogens were isolated from urine, stool, blood, and pus (skin and ear) samples. The percentages of clinical isolates used in this study were: 30% *Escherichia coli*, 30% *Staphylococcus aureus*, 14% *Salmonella typhi*, 13% *Klebsiella pneumoniae* and 13% *Pseudomonas aeruginosa*.

Method and Break Points

Antimicrobial susceptibility test was carried out using the disk diffusion technique (Bauer- Kirby susceptibility test) as described by the National Committee for Clinical Laboratory Standards (NCCLS) (15). The antimicrobial disks contained Cefixime 5µg (CFM 5, Lot No. 622076, expiry date 2011 Jan.) and Cefepime 30µg (FEP 30, Lot No. 627226, expiry date 2011), obtained from Oxoid Ltd; (Basingstoke, Hampshire, England). Zone diameter breakpoints for susceptible and resistant isolates were set

as ≤14 mm (resistant), 15-17mm (intermediate) and ≥ 18mm (susceptible) for cefixime and ≤16 mm (resistant), 17-19mm (intermediate) and ≥20mm (susceptible) for cefepime**(15).**

Selection and Preparation of Media

Mueller-Hinton Agar (Oxoid Ltd; Basingstoke, Hampshire, England) was prepared according to the manufacturer's guide lines and sterilized by autoclaving (121 °C for 15 min). Plates were prepared by pouring freshly prepared, sterilized and cooled agar into flat glass petri dishes (90mm) to a uniform depth of approximately 4mm.

McFarland Turbidity Standard and Preparation of Inoculum

McFarland No. 0.5 standard was prepared (by adding 0.5 ml of 0.048 M barium chloride to 99.5 ml of 0.36N sulfuric acid). With a sterile polyester swab, 4 -5 similar appearing colonies (which were well isolated on primary medium), were transferred to 3 ml trypticase soy broth. The culture tube was incubated at 37°C, for 2 to 6 hours to produce the bacterial suspension turbidity similar to McFarland No. 0.5 standard.

Inoculation

Plates were inoculated within 15 minutes of preparation of suspension; a dry sterile polyester swab was immersed in bacterial suspension and streaked in three directions at approximately 60°angle. Antimicrobial disks were placed using sterile forceps to a suitable distance to avoid overlapping of zones of inhibition. The plates were incubated at 35°C for 16-18 hours.

Interpretation

After that period, the zone appeared around the disks was measured, including the diameter of disk (6mm) using sliding calipers held on the back of the inverted Petri plate to the nearest millimeter. Each zone was compared with known standards (15), and the organisms under test were identified as susceptible or resistant to that particular antibiotic (Table I). Pathogens that showed zones in the range of intermediate resistance (*IR*) are not considered as sensitive or susceptible organisms against the tested antibiotic. The result values ranges in this are usually regarded as indicative of non useful therapeutic options similar to the resistant category for treatment purposes (16).

RESULTS AND DISCUSSION:

As antibiotic resistance reduces treatment efficacy, it is a time to consider routine susceptibility testing to guide individual patient treatment and surveillance of antibiotic resistance (17). An extensive work has been reported by many authors on microbial drug resistance (18- 22). Among different in vitro methods, disk diffusion method has been utilized as a major technique for evaluation of microbial resistance and susceptibility against antibiotics (23-26).

Orally administered cephalosporins, such as cefixime, possess good activity and attains serum concentrations above the MICs for most Enterobacteriaceae (27, 28). In this study, cefixime showed good activity against *E. coli, S .aureus, and K. pneumoniae. E. coli and K. pneumoniae* were isolated from urine samples and *S.aureus* from skin and ear pus cultures of different individuals. It possessed superior activity against *S. typhi* (90%). Out of 20 samples only two specimens showed resistance against cefixime. These two resistant pathogens were separated from the same source that is blood, but from two different individuals. This variation in the zones may because that these two individuals had already been exposed to the same antibiotic many times in the past, either rationally, inappropriately or self medicated, and so resulted in the resistance. The higher activity gives an idea that cefixime may be a drug of choice in the treatment of typhoid fever. Matsumoto *et al.,* in 1999 carried out the study for cefixime against 73 clinical isolates of *S. typhi*; it exhibited excellent activity against reflecting its high beta-lactamase stability (29). Increasing prevalence of multidrug-resistant (MDR) *S. typhi* strains in typhoid fever has been reported. Oral cefixime therapy given as a 12-day regimen (20-30 mg/kg divided twice daily) demonstrated both safety and efficacy and it is most cost effective therapy (30). Cefixime did not show an excellent response against *P. aeruginosa* isolates, out of 18 only 3 samples were susceptible to cefixime. From these three susceptible organisms, two were cultured from ear pus of unlike individuals, and one from skin pus. There are few factors that contribute in variation of resistant range among

individuals. Some of the bacteria acquired in the community are antibiotic resistant and have been carried into the community by people returning from hospital where antibiotic resistant bacteria are more common. Other factors driving towards the emergence and spread of antibiotic resistant bacteria as well as the spread of other bacteria in the community are improper food preparations practices both in home and commercial establishments, inadequate water treatments and inspection, and poor sanitation and hygiene (31). Results of study illustrate the development of resistance in *P.aeruginosa* against the broad spectrum cefixime. Majority of *S. aureus isolates* were resistant to cefixime, 15 isolates from 41 were sensitive, thus giving 63.4% resistance. It is evident from results that cefixime is still effective against *Klebsiella (77.77%)* and possesses strong activity against *S. typhi (90%)*.

Cefepime is relatively a new cephalosporin and shows much less resistance than cefixime. Cefepime is sensitive against all the tested microorganisms, 92.6% against *E. coli*, 85% against *S. aureus*, 65% against *S. typhi*, 94% against *K. pneumonia*, and 77.7% against *P.aeruginosa*, used in this work. Cefepime is not as much effective against *S. typhi* as cefixime. Cefepime is considered as highly potent agent against *E. coli* and *K. pneumoniae* specifically. Only 3 isolates out of 41 *E.coli (all three isolated from urine samples)* and 1 out of 18 *K. pneumoniae (isolated from urine)* did not show sensitive zones (Table 1).

Table 1: Resistance Pattern of CEFEPIME (30µg) and CEFIXME (5µg) Against Different Pathogens

No. of Clinical isolates	SOURCES	CEFIXME (5µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity			Cefepime (30µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity		
			*Resistant (R)** ≤14mm	*Intermediate Resistant (IR)*** 15-17 mm	*Sensitive (S)**** ≥18mm		*Resistant (R)** ≤16mm	*Intermediate Resistant (IR)*** 17-19mm	*Sensitive (S)**** ≥20m
Escherichia coli									
1	URINE	NIL	R			11.2	R		
2	URINE	22	S			19	S		
3	URINE	21	S			20	S		
4	URINE	NIL	R			21	S		
5	URINE	20	S			21	S		
6	URINE	21	S			19	S		
7	URINE	19	S			20	S		
8	URINE	21	S			17	I R		
9	URINE	21	S			23	S		
10	URINE	18	S			NIL	R		
11	URINE	22.5	S			23.5	S		
12	URINE	18	S			22	S		
13	URINE	19	S			23	S		
14	URINE	12	R			20	S		
15	URINE	20	S			20	S		
16	URINE	24	S			21	S		
17	URINE	NIL	R			19	S		
18	URINE	20	S			21	S		

No. of Clinical isolates	SOURCES	CEFIXME (5µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity			Cefepime (30µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity		
			*Resistant (R)** ≤14mm	*Intermediate Resistant (IR)*** 15-17 mm	*Sensitive (S)**** ≥18mm		*Resistant (R)** ≤16mm	*Intermediate Resistant (IR)*** 17-19mm	*Sensitive (S)**** ≥20m
19	URINE	16	I R			22	S		
20	URINE	21	S			23	S		
21	URINE	22	S			20	S		
22	URINE	21	S			14	R		
23	URINE	23	S			23	S		
24	URINE	21	S			19	S		
25	URINE	16	I R			22	S		
26	URINE	22	S			24	S		
27	URINE	20	S			24	S		
28	URINE	19	S			24	S		
29	URINE	NIL	R			25	S		
30	URINE	16	I R			21.8	S		
31	URINE	12	R			22	S		
32	URINE	15	I R			22.5	S		
33	URINE	NIL	R			22	S		
34	URINE	NIL	R			23.5	S		
35	URINE	12	R			21	S		
36	URINE	19	S			31	S		
37	URINE	15	I R			26	S		
38	URINE	23	S			22	S		
39	URINE	21	S			20	S		
40	URINE	20	S			21	S		
41	URINE	22	S			22	S		
Staphylococcus aureus									
42	SKIN PUS	NIL	R			22	S		
43	SKIN PUS	19	S			29	S		
44	SKIN PUS	9	R			22	S		
45	SKIN PUS	NIL	R			29	S		
46	SKIN PUS	NIL	R			27	S		
47	SKIN PUS	22	S			24.5	S		
48	SKIN PUS	12	R			21	S		
49	SKIN PUS	NIL	R			NIL	R		
50	SKIN PUS	10	R			23	S		
51	SKIN PUS	21	S			24	S		

No. of Clinical isolates	SOURCES	CEFIXME (5µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity			Cefepime (30µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity		
			*Resistant (R)** ≤14mm	*Intermediate Resistant (IR)*** 15-17 mm	*Sensitive (S)**** ≥18mm		*Resistant (R)** ≤16mm	*Intermediate Resistant (IR)*** 17-19mm	*Sensitive (S)**** ≥20m
52	SKIN PUS	18		S		19		I S	
53	SKIN PUS	NIL		R		NIL		R	
54	SKIN PUS	20		S		18		I S	
55	SKIN PUS	13		R		19		I S	
56	SKIN PUS	8		R		20		S	
57	SKIN PUS	19		S		20		S	
58	SKIN PUS	NIL		R		NIL		R	
59	SKIN PUS	16		I R		23		S	
60	SKIN PUS	20		S		19		I S	
61	SKIN PUS	7		R		19		I S	
62	SKIN PUS	22		S		NIL		R	
63	SKIN PUS	7		R		23		S	
64	SKIN PUS	15		I R		22		S	
65	SKIN PUS	21		S		22		S	
66	SKIN PUS	10		R		25		S	
67	SKIN PUS	22		S		32		S	
68	EAR PUS	20		S		33		S	
69	EAR PUS	NIL		R		31		S	
70	EAR PUS	21		S		NIL		R	
71	EAR PUS	NIL		R		20		S	
72	EAR PUS	19		S		NIL		R	
73	EAR PUS	NIL		R		23		S	
74	EAR PUS	19		S		32		S	
75	EAR PUS	NIL		R		22		S	
76	EAR PUS	18		S		23		S	
77	EAR PUS	15		I R		23		S	
78	EAR PUS	14		R		26		S	
79	EAR PUS	22		S		21		S	
80	EAR PUS	9		R		19		I S	
81	EAR PUS	15		I R		21		S	
82	EAR PUS	10		R		22		S	
Klebsiella pneumoniae									
83	URINE	23		S		16		R	
84	URINE	12		R		21		S	

No. of Clinical isolates	SOURCES	CEFIXME (5µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity			Cefepime (30µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity		
			*Resistant (R)** ≤14mm	*Intermediate Resistant (IR)*** 15-17 mm	*Sensitive (S)**** ≥18mm		*Resistant (R)** ≤16mm	*Intermediate Resistant (IR)*** 17-19mm	*Sensitive (S)**** ≥20m
85	URINE	22	S			22	S		
86	URINE	28	S			21	S		
87	URINE	13	R			23	S		
88	URINE	20	S			21	S		
89	URINE	22	S			22	S		
90	URINE	NILL	R			25	S		
91	URINE	19	S			22	S		
92	URINE	21	S			25	S		
93	URINE	22	S			21	S		
94	URINE	19	S			22	S		
95	URINE	19	S			20	S		
96	URINE	20	S			24.5	S		
97	URINE	8	R			22.8	S		
98	URINE	19	S			22.5	S		
99	URINE	20	S			25	S		
100	URINE	21	S			22	S		
Pseudomonas aeruginosa									
101	EAR PUS	31	S			23	S		
102	EAR PUS	NIL	R			13	R		
103	EAR PUS	14	R			22	S		
104	EAR PUS	NIL	R			11	R		
105	EAR PUS	NIL	R			27	S		
106	EAR PUS	NIL	R			23	S		
107	EAR PUS	27	S			32	S		
108	EAR PUS	NIL	R			21	S		
109	EAR PUS	NIL	R			22	S		
110	EAR PUS	NIL	R			26	S		
111	EAR PUS	NIL	R			24	S		
112	EAR PUS	NIL	R			33	S		
113	EAR PUS	15	I R			NIL	R		
114	EAR PUS	NIL	R			21	S		
115	SKIN PUS	NIL	R			20	S		
116	SKIN PUS	NIL	R			21	S		
117	SKIN PUS	NIL	R			NIL	R		

No. of Clinical isolates	SOURCES	CEFIXME (5µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity			Cefepime (30µg) *Zone of inhibition (mm)*	Pathogen Shows Resistance/Sensitivity		
			*Resistant (R)** ≤14mm	*Intermediate Resistant (IR)*** 15-17 mm	*Sensitive (S)**** ≥18mm		*Resistant (R)** ≤16mm	*Intermediate Resistant (IR)*** 17-19mm	*Sensitive (S)**** ≥20m
118	SKIN PUS	24	S			20	S		
Salmonella typhi									
119	BLOOD	23	S			34	S		
120	BLOOD	19	S			NIL	R		
121	BLOOD	21	S			29	S		
122	BLOOD	16	I R			16	R		
123	BLOOD	21	S			10	R		
124	BLOOD	21	S			23	S		
125	BLOOD	23	S			17	R		
126	BLOOD	15	I R			19	I S		
127	BLOOD	30	S			22	S		
128	BLOOD	19	S			14	R		
129	BLOOD	26	S			11	R		
130	BLOOD	19	S			24	S		
131	BLOOD	21	S			14	R		
132	BLOOD	24	S			21	S		
133	BLOOD	23	S			22	S		
134	STOOL	23	S			23	S		
135	STOOL	22.5	S			22	S		
136	STOOL	24	S			21	S		
137	STOOL	25	S			24	S		
138	STOOL	18	S			23	S		

*Resistant (R) means pathogens are not responsive to tested antibiotics.

**Intermediate Resistance (IR) is an indication of non useful therapeutic options similar to the resistant category.

***Susceptible (S) means organisms are responsive to tested antibiotics.

In this investigation there is a variation in the zones of inhibition among the same species of pathogens isolated from the same source like blood, urine or skin and ear pus but from different individuals. There are many reasons for this variation of zones like one individual has already been treated with the experimental antibiotic many times earlier before the present study, and hence organism may acquire the resistance as compared to the same pathogen isolated from different culture. In many developing countries like Pakistan, antibiotics are sold as over the counter medicines. Self medication is widespread among the individuals and it is a contributing factor that results in emergence of resistance. Poverty is a another driver in the developing countries where the use of sub-standard medicines are frequent and standard drugs are out of the reach of common population, it encourages the self medication, since they are not able to approach the health care professionals. Low level of literacy results in

inappropriate doses and incomplete treatment. Some times individuals had not followed the course regimen prescribed by the physician; they left the treatment when the symptoms were started to disappear. This incomplete and insufficient exposure of antibiotic to the pathogens also results in the development of resistance. These are the few reasons supposed for variation of zones among the same pathogen even isolated from the same sources. Our study is dealing with the surveillance of anti microbial resistance, future research is strongly recommended to evaluate the accurate reasons for the deviation of zones. Nweneka et al., suggested in his study that the dominant factor in the emergence and spread of antibiotic-resistant bacterial pathogens is the intensive use of antibiotic agents; signifying a strong influence of behavioral factors in the development of antimicrobial resistance, both from prescribers and patients. Despite that antimicrobial consumption facilitates the development of antimicrobial resistance; other complex factors need serious considerations (32). The consequences of resistance are severe. Infections caused by resistant microbes fail to respond to treatment, resulting in prolonged illness and greater risk of death. Treatment failures also lead to longer periods of infectivity.

Cefepime might be utilized as a better choice for the infections caused by *P.aeruginosa*, rather than cefixime which showed poor susceptibility. Although cefixime had good activity against *P. aeruginosa* in the past (33) but its irrational use has led to the high resistance now days. None of the *K. pneumoniae* specimen showed nil zones by cefepime and only one gave no growth with cefixime. Comparatively higher zones were obtained with cefepime than cefixime. The in vitro sensitivity test of these organisms describes that both antibiotics cefepime and cefixime are still effective against different gram positive and gram negative pathogens which cause different blood, skin, ear, stool and urine infections. They must be prescribed reasonably, keeping in mind that development of resistance against cefixime and cefepime may pass on the genes responsible for antibiotic resistance and may appear after couple of years. A comparative resistance pattern of both antibiotics against gram positive and gram negative organisms is shown in *figure 1.*

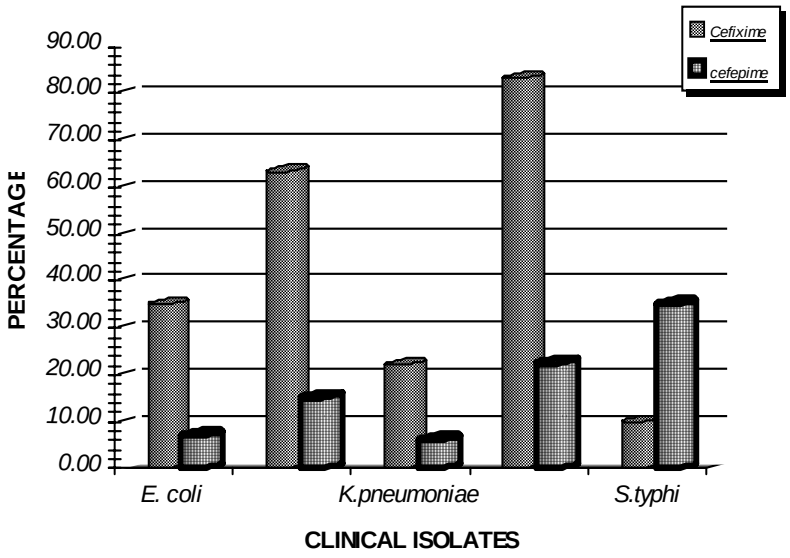

Figure 1: Resistance pattern of Cefixime and Cefepime among different clinical isolates

A difference in susceptibility to antibiotics by microorganisms has become a major factor in drug choice and success of treatment. Great concerns have been raised regarding emerging antimicrobial resistance among bacteria that may result in unpredictable antimicrobial susceptibility and failure of therapy (34, 35).

Information on resistance is needed at local, national, and international levels to guide decision making and responses. Local information should be used in clinical management and to update treatment guidelines, educate prescribers, and guide infection control policies (36). The study revealed that antibiotic resistance has become a significant problem and will continue as bacteria continue to grow under the selective pressure of antibiotics. The development of resistance is an expected consequence of irrational use, self-medication and the incomplete course of antibiotics attributing towards resistance development. If it is going un-controllable, a time will not so far when an effective antibiotic would not be able to treat even minor infections.

CONCLUSION

Drug resistance is one of the nature's never ending processes leading towards treatment failures. The study reveals that the new cefepime, a 4th generation cephalosporin, is a promising antimicrobial agent for various infections caused by *Escherichia coli*, *Staphylococcus aureus , Klebsiella* spp., *Salmonella typhi* and *Pseudomonas aeruginosa* as compared to cefixime, a 3rd generation cephalosporin.

REFERENCES

(1) Smith A. Bacterial resistance to antibiotics. In: Stephen P Denyer, Norman A. Hodges and Sean P (ed) Hugo and Russell's Pharmaceutical microbiology. 7th edition. USA, Blackwell science 2004: 220-222.

(2) Tortora GJ, Funke BR, Case C. Microbiology; an introduction. 9th edition, San Francisco, Pearson Benjamin Cummings, 2007: 587-603.

(3) Finch R. Bacterial resistance to antibiotics. In: Stephen P Denyer, Norman A. Hodges and Sean P (ed) Hugo and Russell's Pharmaceutical microbiology. 7th edition. USA, Blackwell science 2004: 223-225.

(4) Yahav D, Paul M, Fraser A, Sarid N, and Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. Lancet Infect Dis., 2007; 7:338–48.

(5) Levinson W. Review of medical microbiology and immunology. New York McGraw Hill, 2004: 72.

(6) Stone JW, Linong G, Andrews JM, Wise, R. Cefixime, in-vitro activity, pharmacokinetics and tissue penetration. J Antimicrob Chemother., 1989, 23(2):221-8.

(7) Santillán RM., García1 GR, Benavente IH., García EM. Efficacy of Cefixime in the Therapy of Typhoid Fever. Proc. West. Pharmacol. Soc., 2000, 43:65-66.

(8) Memon IA, Billoo AG, Memon HI. Cefixime: an oral option for the treatment of multidrug-resistant enteric fever in children. South Med J., 1997, 90(12):1204-7.

(9) Alfandari S, Bonenfant C, Depretere L, Beaucaire G. Use of 27 parenteral antimicrobial agents in north of France hospitals. Med Mal Infect., 2007; 37: 103–07.

(10) Mutnick AH, Rhomberg PR, Sader HS, Jones RN. Antimicrobial usage and resistance trend relationships from the MYSTIC Programme in North America (1999–2001). J Antimicrob Chemother, 2004; 53: 290–96.

(11) Sanders CC. Cefepime: the next generation? Clin Infect Dis., 1993;17: 369–79.

(12) Chapman TM, Perry CM. "Cefepime: a review of its use in the management of hospitalized patients with pneumonia". Am J Respir Med., 2003 2 (1): 75–107.

(13) Gutierrez K. Pharmacology Review, Newer Antibiotics: Cefepime. NeoReviews, 2004, 5(9)e 382.

(14) Sáez-Llorens X, O'Ryan M. Cefepime in the empiric treatment of meningitis in children. Pediatr Infect Dis., J. 2001, 0(3):356-61.

(15) NCCLS. Performance standards for antimicrobial disk susceptibility tests; Approved standard, 2000, 7th ed., vol 17 (1).

(16) Schwalbe, R, Steele-Moore L, Goodwin.AC. Antimicrobial susceptibility testing protocols, 2007;

Taylor and Francis Group: 62.

(17) McNulty C , Helicobacte PHLS, Owen R, Tompkins D, Hawtin P, McColl K, Price A, Smith G and Teare L. Helicobacter pylori susceptibility testing by disc diffusion. ***Journal of Antimicrobial Chemotherapy***, 2002 49, 601-609.

(18) Bhat KG, Tripathy A, Rajagopal R, Ramachandran S. A simple broth-disk method to determine the minimum inhibitory concentration of ceftriaxone on Salmonella enterica serovar typhi and paratyphi. ***Indian J Pathol Microbiol***. 2009; 52(2):189-90.

(19) Kulah C, Aktas E, Comert F, Ozlu N, Akyar I, Ankarali H. Detecting imipenem resistance in Acinetobacter baumannii by automated systems (BD Phoenix, Microscan WalkAway, Vitek 2); high error rates with Microscan WalkAway. ***BMC Infect Dis***., 2009, 16; 9:30.

(20) Punpanich W, Tantichattanon W, Wongwatcharapaiboon S, Treeratweeraphong V. In vitro susceptibility pattern of cephalosporin-resistant Gram-negative bacteria. ***J Med Assoc Thai.***, 2008; 91 Suppl 3:S21-7.

(21) Harada K, Asai T, Ozawa M, Kojima A, Takahashi T. Farm-level impact of therapeutic antimicrobial use on antimicrobial-resistant populations of Escherichia coli isolates from pigs. ***Microb Drug Resist***., 2008; 14(3):239-44.

(22) Speciale A, Musumeci R, Blandino G, Milazzo I, Caccamo F, Nicoletti G. Minimal inhibitory concentrations and time-kill determination of moxifloxacin against aerobic and anaerobic isolates. ***Int J Antimicrob Agents***, 2002; 19(2):111-8.

(23) Dambrauskiene A, Adukauskiene D, Jeroch J, Vitkauskiene A. Pseudomonas aeruginosa bacteremia: associations with a source of infection and antibiotic resistance. ***Medicina (Kaunas),*** 2009; 45(1):1-7.

(24) Bettin A, Suárez P, Bedoya A, Reyes N. Staphylococcus aureus in residents from a nursing-home in Cartagena. ***Rev Salud Publica (Bogota),*** 2008; 10(4):650-7.

(25) Kum C, Kirkan S, Sekkin S, Akar F, Boyacioglu M. Comparison of in vitro antimicrobial susceptibility in Flavobacterium psychrophilum isolated from rainbow trout fry**.** ***J Aquat Anim Health***, 2008; 20(4):245-51.

(26) Niebla A, González I, Vallín C. Antimicrobial activity of beta-lactams against multiresistant micro-organisms from the family Enterobacteriaceae, and genus Pseudomonas. ***Microbios***., 1994;80(325):245-50

(27) Edlund C, Nord CE. Effect on the human normal microflora of oral antibiotics for treatment of urinary tract infections. ***J Antimicrob Chemother***., 2000; 46 Suppl 1:41-8; discussion 63-5.

(28) Janknegt R, van der Meer JW. Sequential therapy with intravenous and oral cephalosporins. ***J Antimicrob Chemother.,*** 1994; 33(1):169-77.

(29) Matsumoto Y, Ikemoto A, Tawara S. Antibacterial activity of cefixime against Salmonella typhi and applicability of Etest**.** ***J Infect Chemother***., 1999; 5(3):176-179.

(30) Girgis NI, Tribble DR, Sultan Y, Farid Z. Short course chemotherapy with cefixime in children with multi drug-resistant Salmonella typhi Septicaemia. ***Pediatr Infect Dis J***., 1995; 14(7):603-5.

(31) Impacts of antibiotic-resistant bacteria, OTA -H-629. 1995. U.S. Congress, Office of technology assessment. Washington DC.,pp:05.

(32) Nweneka CV' Tapha-Sosseh N, Sosa A. Curbing the menace of antimicrobial resistance in developing countries. ***Harm Reduction Journal,*** 2009, 6**:**31.

(33) Kumamoto Y, Hirose T, Tanaka N, Hikichi Y, Shigeta S, Shiraiwa Y, Kameoka H, Yoshida H, Ogata M, Tazaki H, et al. Comparative studies on activities of antimicrobial agents against causative organisms isolated from urinary tract infections (1989). III. Secular changes in susceptibility**.** ***Jpn J Antibiot***., 1995; 48(9):1174-263.

(34) Huang TM, Lin TL, Wu CC. Antimicrobial susceptibility and resistance of chicken Escherichia coli, Salmonella spp., and Pasteurella multocida isolates. ***Avian Dis***., 2009. 53(1):89-93.

(35) Khameneh ZR, Afshar AT. Antimicrobial susceptibility pattern of urinary tract pathogens. ***Saudi J Kidney Dis Transpl.,*** 2009; 20(2):251-3.

(36) Williams RJ, Ryan MJ, Surveillance of antimicrobial resistance an international perspective. *BMJ* 1998; 317:651-660.

دراسة مقارنة لأنماط مقاومة مسببات الأمراض ضد Cefepime و Cefixime

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ملخـص

أدى الإستخدام الخاطئ للمضادات الحيوية إلى زيادة مقاومة الجراثيم للأدوية مما أدى إلى الاعتقاد بأن عصر المضادات الحيوية قارب على الإنتهاء.إن تقييم فعالية المضادات الحيوية أمر هام لضمان الحصول على نتائج جيدة للعلاج. والغرض من هذه الدراسة تقييم مقاومة غزلات ضد cefixime (من الجيل الثالث للسيفالورسبورين) و Cefepime (من الجيل الرابع للسيفالوسبورين). وتسجل الدراسة 138 عزلة سريرية منها (30%) *Escherichia coli* و(30%) *Staphlococcus aureus* و (14%) *Salmonella typhi* و (13%) *Klebsiella pneumoniae* و (13%) *Pseudomonas aeruginosa* وقد تم تجميع العزلات خلال سنة (من كانون الثاني 2008 – كانون الثاني 2009) من مختبرات علم الأمراض من مستشفيات مختلفة في كراتشي/ باكستان وتسجيل 59 عينة بول ، 30عينة قيح جلدي ، 29 عينة قيح أذني ، 15عينة دم ، و 5عينات براز، تحت دراسة الحساسية للمضادات الحيوية خارج الجسم باستخدام المعيار McFarland 0.5 .

أظهرت النتائج أن Cefepime كان له تأثير على 92.6% *Escherichia coli* ، 85%*Staphlococcus aureus* ،94% *Klebsiella pneumoniae* ، 77.77% *Pseudomonas aeruginosa* و 65% *Salmonella typhi*.

Cefexime كان أقل فعالية ضد *Pseudomonas aeruginosa* (16.66%) بينما ظهرت الفعالية الأفضل تجاه *Salmonella typhi* (90%). يخلص البحث إلى ضرورة السعي لتعزيز الجهود المرافقة للمحافظة على فعالية هذه المجموعات الدوائية ضد استمرارية تكوين سلالات مقاومة لها.

الكلمات الدالة: سيفيكسيم، سيفيبيم، طريقة انتشار القرص، مقاومة الجراثيم، ممرض، كراتشي، باكستان.

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