World Journal of Pharmaceutical research

Volume 2, Issue 5, 1238-1253. Research Article ISSN 2277 – 7105

URINARY TRACT INFECTIONS CAUSED BY *PSEUDOMONAS, KLEBSIELLA AND PROTEUS* SPECIES: A 2005-2009 SURVEY OF TRENDS IN THEIR INFECTIVITIES AND SUSCEPTIBILITIES TO SELECTED FLUOROQUINOLONES IN A TERTIARY HOSPITAL IN NIGERIA

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Article Received on
10 June 2013,

Revised on 16 July 2013,
Accepted on 20 August 2013

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ABSTRACT

Fluoroquinolones (FQs) have become agents of therapeutic interest since it is one of the few anti-infective treatment options in many regions. This study examines trends in the activities of the FQs to some Urinary Tract Infection (UTI) pathogens with multi-drug resistances that are often difficult to treat; so as to identify the changing pattern in pathogen's infectivity or susceptibilities to FQs, investigate multi-FQs resistance patterns and the inter-activity relations of the FQs. Of the 1590 UTI pathogens isolated between 2005 and 2009, *Klebsiella* spp, *Proteus* spp and *Pseudomonas* spp accounted for 10%, 4.7% and 3.0% respectively; making them to rank third, fourth and fifth most infectious UTI pathogens in the region. The susceptibilities changes (decrease) of UTI *Klebsiella spp* with ciprofloxacin, ofloxacin, pefloxacin, and nalidixic acid were 7.6%, 4.3%, 11.5% and 19.7% respectively. The activities of ofloxacin was significantly higher ($P<0.05$) than ciprofloxacin in pefloxacin-resistant *Klebsiella*. A 37.5% decrease in ciprofloxacin activities against *Proteus spp* were recorded but pefloxacin activities appreciated by 11.5% during the 5 year periods. Ciprofloxacin and ofloxacin recorded uniform activities of 58.9% each against nalidixic acid-resistant *Proteus* UTI isolates. The susceptibility of *Pseudomonas* increased from 20% in 2005 to 75% in 2009. Resistance rates to three and four quinolones were respectively 18.9% and 11.3% for *Klebsiella;* 31.7% and

20.8% for *Pseudomonas* but 10.8% each for *Proteus* spp. Resistances to *Pseudomonas, Proteus and Klesiella* spp have exceeded 20% and newer agents may be required to treat some cases because multi-FQs resistant pathogenic isolates are on the increase.

KEY WORDS: Urinary Tract Infections, *Pseudomonas* UTI, Nalidixic acid-resistant *Klebsiella*, co-quinolone resistance, fluoroquinolone, ciprofloxacin.

INTRODUCTION

Urinary tract infections (UTIs) are common conditions that affect both outpatients and inpatients. The clinical signs and symptoms could include burning sensation during urination, frequent or intense urges to urinate, backaches, lower abdomen pain, fever or chill, and cloudy, dark, bloody, or unusual-smelling urine.

The global prevalence of the disease was put that 150 million cases per year (Stamm and Norby, 2001). In America alone, about eight million cases necessitated visits to physician (Warren *et al*, 1999) while1.5 million and 0.3 million cases are respectively attributed to emergency room visits and hospital admission annually with about 3.5 billion dollar cost annually (Foxman, 2003; Litwin *et al*., 2005).

Many factors including age, sex, cultures, sexual hygiene, obstruction of the urinary tract, toilet wiping method, use of irritant soap, vagina deodorant and contraceptives are reported to predispose to UTI but the involvement of pathogens like *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* have a high preponderance for catheter use (Chang *et al*., 1990; Jarvis and Martone, 1992; Hootan, 2001). In addition, UTI caused by these pathogens vary slightly between outpatients and Inpatients. For instance, *Pseudomonas* UTI accounted for 0-4% and 1-11% cases in out-patient and inpatients respectively while the corresponding values for UTI was determined to range 6-12% versus 6-15% for *Klebsiella* and 4-6% versus 4-8% for *Proteus* (Neal, 2011). Many medical conditions such as diabetes, sickle cell anemia, neurogenic bladder, urinary tract abnormalities and kidney stones can put individuals at risk for urinary tract infections (UMMC, 2013) and as opportunistic pathogens, they may also attack hospitalized immune-compromised patients or patient with severe underlying diseases like diabetes mellitus or chronic pulmonary obstruction (Podschun and Ullmann, 1998). But generally, It is estimated that *Klebsiella* spp cause 8% of all nosocomial bacterial infections in the United States and in Europe (Podschun and Ullmann, 1998) and is ranked as the eighth most important infectious pathogens in hospitals in the United States.

Depending on site of isolates and infection, many virulence factors may be associated with many pathogens. The virulence of *Pseudomonas aeruginosa* isolated from several sites are multifactorial and can include cell associated factors like alginate, lipopolysaccharide, flagellum, pilus and non-pilusadhesins and/or exoenzymes or secretory virulence factors like protease, elastase, phopholipase, pyocyanin, exotoxin A, exoenzyme S, hemolysins (rhamnolipids) and siderophores (Zulianello *et al*., 2006; Veesenmeyer *et al*., 2009). In particular, elastase, protease are reported in *P.aeruginosa* associated UTI (Woods *et al*., 1986) while *Proteus* spp can cause urease production which it hydrolysis to ammonia to form alkaline urine for its environmental survival and together with the fimbriae can lead to upper urinary tract infections (Struble, 2013).

The defects in the anatomical structures, vesicouretic reflux, obstruction, surgery, metabolic diseases like diabetes mellitus and immunosuppression in patient of organ transplant are predisposing factors associated with complicated UTI (Leone *et al*., 2003). However *P. aeruginosa* may account for about 10% of all hospital-acquired infections, particularly pneumonia, urinary tract infections, surgical wound infections and bloodstream infections. Urinary tract infections can cause serious medical conditions that may affect the function of the kidney or cause irreparable damage to the kidneys (Curtis, 2013). Although most UTIs may be associated majorly with *Escherichia coli* but *klebsiella* associated UTIs always result to complicated cases and can be resistant to many antibiotics and thereby requiring specialized treatment (Curtis, 2013). *Klebsiella* pathogen may get to the urinary tract system from the intestinal tract where the bacteria multiply to cause pain and irritation (Curtis, 2013).

Although the genus *Klebsiella* bacteria are widely distributed in nature with habitat in the soil, water and as well as part of the normal flora of the intestinal tract, but some *Klebsiella* spp, especially strains of the species *Klebsiella pneumoniae*, are opportunistic pathogens that can cause pneumonia, urinary tract infections, and bacteremia. There is however as increase in *Klebsiella* infections, especially in hospitals and due to multiple-antibiotic resistant strains. *Klebsiella* is the cause of about 10% of urinary tract infections in humans. The strain is resistant to many antibiotics, including ampicillin, ticarcillin, trimethoprim-sulfamethoxazole, and gentamicin, but is susceptible to amikacin, ciprofloxacin, and imipenem.

Pathogenic bacteria get to the urinary tract through many ways including regular sexual intercourse and anal routes owing to the proximity of the urethra to anal region. However, pregnant women are more susceptible to kidney infection because as the uterus enlarges it compresses the ureters and bladder. This causes urine to back up into the kidney, increasing the risk of bacterial infection (UMMC, 2013).

Although *Klebsiella* pathogenicity factors such as capsules or lipopolysaccharides could be gainfully worked upon to develop vaccination against that may serve as immunological infection control measures, but antibiotics use still remain the mainstay in the chemotherapy of most pathogenic bacteria including *Klebsiella* species. However previous studies of pathogenic bacteria from various infectious sites have demonstrated widespread of resistances to several anti-bacterial agents making the fluoroquinolones as one of the few treatment options in the region. But resistance to fluoroquinolones has been on the increasing trends in many regions since their introduction for UTI treatment. Many regions have recorded high resistances of pathogens to the fluoroquinolones. For instance, the incidence of pathogen's resistance to ciprofloxacin in China increased by about 13% within a span of 5 years (Shao, 2003) while higher values were obtained in places like Spain (14%) and Bangladesh (26.0%) (Iqbal *et al*., 1997; Kahlmeter, 2003). Fluoroquinolones are widely prescribed by physicians on one hand since they are one of the today's effective classes of agents and widely misuse through self medication by patients on the other hand since patients have an unlimited or uncontrolled access to them in many regions. In this present study, survey of trends in the resistances of pathogen to the fluoroquinolones class of drug was made so as to guide clinical decision making in terms of their empiric choices as well as to provide clinical information for local policy formulations in respect to utilization for UTIs or other infections in the region.

AIMS AND OBJECTIVES

The study was aimed at investigating trends in urinary tract infection caused by *Pseudomonas, Klebsiella and Proteus spp*, the changing patterns of the activities of the fluoroquinolones against these UTI pathogens and to investigate the inter-activity relations of the fluoroquinolones from 2005 to 2009.

MATERIALS AND METHOD

Sampling

1590 cases of urinary tract infections comprising 785 males and 805 females aged below 1year to 95 years were assessed between January 2005 and December 2009 in individuals suspected to have UTI following the presented clinical signs/symptoms and confirmed with microbiological assay their urine specimens.

Urine culture and Sensitivity Assay

Midstream urine samples were obtained from patients with suspected urinary tract infection into clean urine specimen bottles previously sterilized. Urine samples were cultured in Eosin-Methylene-Blue Agar (EMB) and incubated at 37^{o}C for 48 hours. Pathogens were isolated and identified using gram staining, morphology and biochemical characters. Only samples with CFU greater than 10^{5} /milliliter were considered to be significant bacteruria as determined by the Laboratory medical microbiologist. Antimicrobial sensitivities were performed with nalidixic acid and fluoroquinolones agents like norfloxacin, pefloxacin, ciprofloxacin and ofloxacin using the Kirby Bauer Disc Diffusion Method in accordance with the Clinical Laboratory Standards Institute (CLSI).

Statistical analysis

Chi square was performed to determine the level of significant difference between the activities of two or more agents at $P<0.05$ significant values. Mean values and standard deviation were determined using Microsoft Excel.

RESULTS AND DISCUSSION

Age and gender distribution of patients

Table 1: Age and gender distribution of patient with UTI caused by *Klebsiella, Proteus and Pseudomonas spp*

Age Range (Yrs)	*Klebsiella* spp		*Pseudomonas* spp		*Proteus* spp		Total (%)
	male	female	male	female	male	female	
0.01-10.0	17	12	2	2	10	0	43 (15.3)
10.01-20.0	8	8	5	5	2	5	33(11.70
20.01-30.0	18	20	4	5	6	7	60 (21.4)
30.01-40.0	7	19	3	2	6	4	41(14.6)

40.01-50.0	8	7	1	0	8	3	27 (9.6)
50.01-60.0	8	3	1	0	7	1	20 (7.1)
60.01-70.0	12	1	13	1	8	2	37 (13.2)
70.01-80.0	8	1	2	1	2	2	16 (5.7)
80.01-90.0	2	0	1	0	1	0	4 (1.4)
Total (%)	88(52.2)	71(44.8)	32(66.7)	16(33.3)	50(67.6)	24 (32.4)	281 (100)
overall Total	159 (56.6%)		48 (17.1%)		74 (26.3%)		

The frequency distribution of age of the patients with UTI caused by *Klebsiella, Proteus* and *Pseudomonas* spp is as shown in Table 1. The result showed that the distribution for patients with *Klebsiella* UTI for the male is multimodal with the mean and standard deviation of 36.94 ± 24.44 years while that of the female is skewed toward low frequency of higher age range with a mean and standard deviation of 27.68 ± 15.71 years. In contrast to the results obtained in both genders for patients with *Klebsiella* UTI, the distribution of patients with *Pseudomonas* associated UTI among the male patients is skewed toward low frequency of lower age range with a mean and standard deviation of 55.24 ± 26.68 years while that of the female is bimodal and is skewed towards low frequency of higher age range (Table 1) with a mean and standard deviation of 26.26 ± 18.67 years. The distribution of male patients who presented with *Proteus* UTI has a mean and standard deviation of 38.81 ± 22.88 years while that of the female is skewed toward lower frequency of higher age range with a mean and standard deviation of 35.84 ± 18.71 years.

The peak year for *Klebsiella* UTI cases was observed in patients who are 20-30 years in both genders but while this age range recorded the highest *Proteus* UTI cases among the female, children who are under 10 years indicated the highest *Proteus* cases among the male patients. Among patients who are above 50 years, UTI cases were consistently higher in male patients of those who are 60-70 years for all the pathogens. Epidemiological survey is consistent with higher cases of UTI observed in this study in those between 20 to 50 years. The higher incidence of UTI in male than female of those below 10 years is also in agreement with the literatures.

Klebsiella, Proteus and Pseudomonas associated UTI cases

Table 2: Distribution pattern of some isolated uropathogenic bacteria from 2005 to 2009

Urinary Tract Isolated Pathogens	Number and Percentage (%) Isolated per Year					Total (%)
	2005	2006	2007	2008	2009	
Klebsiella spp	14 (8.8)	35 (15.9)	31 (19.5)	37 (23.3)	42 (26.4)	159 (100)
Proteus spp	7 (9.5)	14 (18.9)	18 (24.3)	18 (24.3)	17 (23.0)	74 (100)
Pseudomonas spp	5 (10.4)	12 (25.0)	6 (12.5)	9 (18.8)	16 (33.3)	48 (100)
Total (%)	26 (9.25)	61 (21.71)	55 (19.57)	64 (22.78)	75 (26.69)	281 (100)

The trend in the yearly distribution of *Klebsiella, Pseudomonas and Proteus* UTI is as shown in Table 2. The increased in infection caused by *Klebsiella* spp between 2005 and 2009 (8.8% to 26.4%) indicated significant correlation during these period. Although *Escherichia coli* and *Staphylococcus aureus* were the major UTI pathogens in the region, however, the involvements of other agents such as *Klebsiella, Pseudomonas and proteus* spp similarly constituted health challenges particularly because of the increasing trends in their UTI infectivity as well as their multi-drugs resistant pattern. Out of the 1590 UTI pathogens isolated between 2005 and 2009, *Klebsiella* spp, *Proteus* spp and *Pseudomonas* spp accounted for 10%, 4.7% and 3.0% respectively and making them to respectively rank third, fourth and fifth most infectious UTI pathogens in the region. *Klebsiella* UTI were reported to rank second in most part of the world (Azra, 2007; Memon, 2007) and lower proportions than our study are reported in China (Shao *et al*., 2003) and in Sukker-City (Memon, 2007) though higher rates of 20.95% are reported in a region in India (Barate and Ukesh, 2012). The reported cases of *Proteus* UTIs (4.9%) in Sukkur-City (Memon, 2007) is similar to pattern obtained in this present study but lower than the 9.52% reported by Barate and Ukesh (2012) in India.

The least UTI infectivity rates were recorded for all agents in year 2005 but *Klebsiella* and *Proteus* species' infectivity peaked in 2009. *Klebsiella* UTI significantly increased from 8.8% in 2005 to 26.4 % in 2009. During similar periods, *Proteus* and *Pseudomonas* UTIs increased from 9.4% to 23.0% and 10.4% to 33.3% respectively. The progressive increase in *Klebsiella* UTI cases between 2005 and 2009 was significantly correlated as the year increases ($P<0.05$) but *Proteus* UTI appeared to plateau from 2007 to 2007. Although the proportions of these

uropathogenic isolates are similar to values obtained in Canada (Karlowsky *et al*., 2011), but the 17.6% rise in *Klebsiella* UTI recorded between 2005 and 2009 in this study creates a worrisome situation when compared to the slower rate of rise within similar period in places like Bangladesh (4.37%) (Saleh *et al*., 2009).

Uropathogenic Klebsiella spp susceptibilities pattern to quinolones

Table 3: Percentage susceptibilities (%) of *Klebsiella spp* to some quinolones

Quinolone Antibiotics	YEARS					TOTAL (%)
	2005	2006	2007	2008	2009	
Ciprofloxacin	71.4 n=14	74.3 n=35	74.2 n=31	52.6n=38	66.7 n=39	66.9 n=157
Ofloxacin	64.3 n=14	75.6 n=33	73.3 n=30	75.6n=33	60.0 n=40	70.0 n=150
Pefloxacin	64.3 n=14	72.7 n=33	67.9 n=28	31 n=29	52.8 n=36	57.1 n=140
Norfloxacin	- -	0.0 n=2	66.7 n=3	25.0 n=8	33.3 n=3	31.3 n=16
Nalidixic acid	25.0 n=12	10.3 n=29	10.7 n=28	0.0 n=28	5.3 n=38	8.1 n=135

The susceptibilities of *Klebsiella* spp to the fluoroquinolones are as shown in Table 3. There are no appreciable changes with ciprofloxacin between 2005 and 2007 neither did ofloxacin's activities significantly varied between 2006 and 2008 while further changes occurring in both drugs recorded no significant difference. Pefloxacin recorded it least activity in 2008 but the greatest losses over time were recorded with nalidixic acid since it lacks the fluorine substituent atom that confers higher activities to the quinolones. These results showed that decrease susceptibilities changes occurring between 2005 and 2009 with ciprofloxacin, ofloxacin, pefloxacin, and nalidixic acid were 7.6%, 4.3%, 11.5% and 19.7% respectively. Many fluoroquinolones are similarly reported to show increasing resistance to uropathogenic *Klebsiella*. For instance, the 7.6% loss in ciprofloxacin activities in this present studies is lower than the 35.12% reported in Bangladesh during a similar period (Saleh *et al*., 2009).

Inter-activities relation of the quinolone antibiotics to UTI Klebsiella isolates

Table 4: Comparison of activities of Quinolones to resistant uropathogenic *Klebsiella spp.*

No. of *Klebsiella spp* Resistant to	**Nos (%) of Resistance *Klebsiella spp* that are sensitive to other quinolones**			
	Nalidixic acid	**Pefloxacin**	**Ciprofloxacin**	**Ofloxacin**
Nalidixic acid (n=111)	XXX	55 (49.5%)	71 (64.0%)	77 (69.4%)
Pefloxacin (n=57)	1 (1.8%)	XXX	17 (29.8%)	27 (47.4%)
Ciprofloxacin (n=48)	1 (2.1%)	5 (10.4%)	XXX	24 (50.0%)
Ofloxacin (n=42)	1 (2.4%)	9 (21.4%)	18 (42.9%)	XXX

The inter-activity relations of the quinolone antibiotics to UTI *Klebsiella* isolates are as shown in Table 4. The activities of ofloxacin against nalidixic acid-resistant-*Klebsiella* spp isolates were slightly higher than ciprofloxacin but its higher activities against pefloxacin-resistant UTI *Klebsiella* were significantly higher ($P<0.05$) than ciprofloxacin. Furthermore, while 50% of ciprofloxacin resistant *Klebsiella* spp were sensitive to ofloxacin, only 42.9% of ofloxacin resistant-*Klebsiella* were on the other hand sensitive to ciprofloxacin. This pattern of result indicated that ofloxacin may have a superior activity on the average over other quinolones routinely used in the region; however, the high rate of cross resistances recorded here is worrisome since it implies that several UTI *Klebsiella* bacteria isolates untreatable by the commonly available fluoroquinolones in the region have emerged. Susceptibility of uropathogens to flouroquinolones was similarly reported to be decreasing in hospitalized patients in Pakistan (Muhammad *et al.*, 2010).

Table 5: Percentage susceptibilities (%) of *Proteus spp* to some quinolones

Quinolone Antibiotics	YEARS					TOTAL (%)
	2005	2006	2007	2008	2009	
Ciprofloxacin	87.5 n=8	66.7 n=12	81.3 n=16	56.3 n=16	50.0 n=18	65.7 n=70
Ofloxacin	66.7 n=6	60.0 n=10	62.5 n=16	76.9 n=13	60.0 n=15	65.0 n=60
Pefloxacin	50.0 n=6	37.5 n=8	60.0 n=15	31.3 n=16	61.5 n=13	48.3 n=58
Norfloxacin	66.7 n=3	0.0 n=5	100 n=1	50.0 n=2	25.0 n=4	33.3 n=15
Nalidixic acid	20.0 n=5	0.0 n=7	12.5 n=16	0.0 n=15	7.7 n=13	7.1 n=56

Uropathogenic Proteus spp susceptibilities Pattern to quinolones

The results of the susceptibility of UTI *Proteus* spp isolates to the fluoroquinolones are shown in Table 5. The activities of ciprofloxacin were consistently higher than ofloxacin from 2005 to 2007 before reversal in trends was observed. Peak activities of nalidixic acid (20.0%) were recorded in 2005. The activities of ciprofloxacin ranges from 50% in 2009 to 87.5% in 2005 while that of ofloxacin ranges between 60% and 76.9%. Ciprofloxacin recorded a 37.5% decline in its activities against *Proteus* spp between 2005 and 2009. Although the corresponding changes (decrease) for other agents were 6.7%, 41.7% and 13.3% respectively for ofloxacin, pefloxacin, norfloxacin and nalidixic acid respectively, but pefloxacin activities appeared to appreciate by 11.5% during similar periods. However, the general activities of all agents except ofloxacin were poor right from 2008.

Inter-activity relations of the quinolone antibiotics to UTI Proteus spp isolates

The inter-activity relations of the quinolone antibiotics to UTI *Proteus* spp isolates is as shown in Table 6.The activities of ciprofloxacin and ofloxacin against nalidixic acid-resistant *Proteus* spp are uniform while the variation in their activities against pefloxacin-resistant *Proteus* spp is not significant. Similarly there was no significant difference between the activities of ofloxacin (29.6%) against ciprofloxacin-resistant *Proteus* spp and that of ciprofloxacin (30.4%) against ofloxacin resistant *Proteus* spp which suggest that both agents may have similar activity profile when resistant are encountered with other fluoroquinolones use in *Proteus* associated UTI in the region.

Table 6: Comparison of activities of Quinolones to resistant uropathogenic *Proteus spp*

No. of *Proteus spp* Resistance to	**No. (%) of Resistance *Proteus spp* that are sensitive to other quinolones**				
	Nal. acid	**Norfloxacin**	**Pefloxacin**	**Ciprofloxacin**	**Ofloxacin**
Nalidixic acid(n=56)	XXX	0 (0.0%)	21 (37.5%)	33 (58.9%)	33(58.9%)
Norfloxacin (n=10)	0 (0.0%)	XXX	0 (0.0%)	4 (40.0%)	1 (10.0%)
Pefloxacin (n=31)	0 (0.0%)	0 (0.0%)	XXX	13 (41.9%)	12(38.7%)
Ciprofloxacin(n=27)	0 (0.0%)	0 (0.0%)	4 (14.8%)	XXX	8 (29.6%)
Ofloxacin (n=23)	0 (0.0%)	0 (0.0%)	4 (17.4%)	7 (30.4%)	XXX

Uropathogenic Pseudomonas spp susceptibilities Pattern to quinolones

Table 7: Percentage susceptibilities (%) of *Pseudomonas spp* to some quinolones

Quinolone antibiotics	YEARS					Total (%)
	2005	2006	2007	2008	2009	
Ciprofloxacin	20.0 n=5	41.7 n=12	66.7 n=6	55.6 n=9	75.0 n=16	56.3 n=48
Ofloxacin	50.0 n=4	54.5 n=11	50.0 n=6	44.4 n=9	66.7 n=15	55.6 n=45
Pefloxacin	25.0 n=4	60.0 n=10	50.0 n=4	57.1 n=7	40.0 n=15	47.5 n=40
Norfloxacin	0.0 n=1	0.0 n=1	- -	0.0 n=2	0.0 n=1	0.0 n=5
Nalidixic acid	0.0 n=4	22.2 n=9	40.0 n=5	14.3 n=7	7.1 n=14	15.4 n=39

The susceptibility of *Pseudomonas* spp to the quinolones is as shown in Table 7. *Pseudomonas* infections represent some of the most difficult conditions to treat in clinical practice which is reflected by the general poor activities of all agents at all times except ciprofloxacin in 2009. However, while the activities of ciprofloxacin against this pathogen increases from 20% in 2005 to 75% in 2009 ($P<0.05$), that of ofloxacin recorded no significant changes before 2008 but increases thereafter in 2009. The activity of pefloxacin against *Pseudomonas* having a range of 25% in 2005 to 60% in 2006 was generally not impressive. Nalidixic acid recorded its highest activity (40%) in 2007. This result appeared encouraging when compared with a 25% resistance growth of *Pseudomonas* over a decade periods reported in a study in USA (Zervos, 2003). This notwithstanding, these results may have demonstrated that several *Pseudomonas* associated UTI in the region are still untreatable with the currently available quinolones in the region.

Inter-activity relations of the quinolone antibiotics to UTI Pseudomonas spp isolates

Table 8: Comparison of activities of Quinolones to resistant uropathogenic *Pseudomonas spp*

No. of *Pseudomonas spp* Resistance to	No. (%) of Resistance *Pseudomonas spp* that are sensitive to other quinolones				
	Nal. acid	Norfloxacin	Pefloxacin	Ciprofloxacin	Ofloxacin
Nalidixic acid (n=32)	XXX	0 (0.0%)	8 (25.0%)	19 (59.4%)	14 (43.8%)
Norfloxacin (n=5)	0 (0.0%)	XXX	0 (0.0%)	2 (40.0%)	3 (60.0%)
Pefloxacin (n=23)	0 (0.0%)	0 (0.0%)	XXX	12 (52.2%)	8 (34.8%)
Ciprofloxacin	1 (5.0%)	0 (0.0%)	5 (25.0%)	XXX	9 (45.0%)

(n=20)					
Ofloxacin (n=20)	1 (5.0%)	0 (0.0%)	5 (25.0%)	10 (50.0%)	XXX

The Inter-activity relations of the quinolone antibiotics to UTI *Pseudomonas* spp isolate are as shown in Table 8. The results showed that multi-FQs-resistant cases are widespread judging from low inter-activities of these antimicrobial agents. Although ciprofloxacin recorded higher activities against nalidixic acid-resistant *Pseudomonas* compare to ofloxacin, the reverse was the case with norfloxacin-resistant *Pseudomonas* spp. These results showed a high rate of cross resistances between the fluoroquinolones in the region. Furthermore, while about half of ofloxacin-resistant *Pseudomonas* may be treated with ciprofloxacin, less than half of ciprofloxacin-resistant *Pseudomonas* may only show susceptibility to ofloxacin but this variation showed no statistical significant.

Uropathogenic coliforms (unclassified) susceptibilities Pattern to quinolones

Table 8: Susceptibilities (%) of unclassified coliforms to some quinolone antibiotics

Agents	YEARS					TOTAL (%)
	2005	2006	2007	2008	2009	
Cipro	89.7 n=39	74.7 n=79	70.0 n=66	76.2 n=122	59.2 n=125	71.2 n=431
Ofloxacin	60.5 n=38	82.3 n=79	79.4 n=68	75.0 n=96	64.8 n=108	78.9 n=389
Pefloxacin	56.6 n=33	73.5 n=68	58.9 n=56	63.2 n=106	50.0 n=104	80.2 n=367
Norflo	14.3 n=7	33.3 n=6	66.7 n=3	41.4 n=29	14.3 n=21	28.8 n=66
Nal. acid	12.5 n=24	19.4 n=72	16.4 n=61	19.5 n=87	2.8 n=108	13.4 n=352

Key: Cipro=ciprofloxacin, Norflo=norfloxacin, Nal. Acid= nalidixic acid

The result of the susceptibility of some coliforms bacteria that were not characterized is as shown in Table 8. Changes occurring between 2006 to 2008 for ciprofloxacin and ofloxacin were not significant but all agents recorded low activities in 2009. The activities of pefloxacin ranges between 50 % and 73.5% while that of norfloxacin ranges between 14.3% and 66.7%. The resistances of all agents with the exception of ciprofloxacin in 2005 and ofloxacin in 2006 have exceeded the below 20% benchmark limit recommendation for some agents in certain guidelines (Gupta *et al.*, 2011). Nalidixic acid whose activity ranges from 2.8% to 19.2% recorded the least during these study periods.

Multi-quinolones resistance patterns of uropathogenic bacteria

The results of multi-quinolone resistances to *Klebsiella, Proteus and Pseudomonas* co-resistance are as shown in Table 8. Resistances to two quinolones were 19.5%, 16.2% and 20.8% respectively for *Klebsiella, Proteus* and *Pseudomonas* respectively. The equivalent values for three and four quinolones were 18.9%, 10.8% and 31.7%; and 11.3, 10.8 and 20.8% respectively for these UTI pathogens.

Table 9: Uropathogens resistance to co-quinolone

***Klebsiella* spp**						**Total (%)**
No. of co-quinolone resistance	**2005 (%)**	**2006 (%)**	**2007 (%)**	**2008 (%)**	**2009 (%)**	
2	1 (7.1)	7 (20.0)	7 (22.6)	7 (18.9)	9 (21.4)	31 (19.5)
3	4 (28.6)	3 (8.6)	5 (16.1)	10 (27.0)	8 (19.0)	30 (18.9)
4	2 (14.3)	4 (11.4)	2 (6.5)	5 (13.5)	5 (11.9)	18 (11.3)
Total (%)	7 (50.0)	14 (40.0)	14 (45.2)	22 (59.5)	22 (52.4)	79 (49.7)
Proteus spp						
2	2 (28.6)	3 (21.3)	2 (11.1)	4 (22.2)	1 (5.9)	12 (16.2)
3	2 (28.6)	3 (21.3)	4 (22.2)	4 (22.2)	6 (35.3)	19 (25.7)
4	0 (0.0)	2 (14.3)	2 (11.1)	1 (5.6)	3 (17.6)	8 (10.8)
Total (%)	4 (57.1)	8 (57.1)	8 (44.4)	9 (50.0)	10 (58.8)	39 (52.7)
Pseudomonas spp						
2	1 (20.0)	1 (8.3)	1 (16.7)	3 (33.3)	4 (25.0)	10 (20.8)
3	2 (40.0)	5 (41.7)	3 (50.0)	2 (22.2)	3 (18.8)	15 (31.3)
4	1 (20)	3 (25.0)	2 (33.3)	2 (22.2)	2 (12.5)	10 (20.8)
Total (%)	4 (80)	9 (75.0)	6 (100)	7 (77.7)	9 (56.3)	35 (72.9)

Klebsiella multi-quinolone resistance ranges from 40.0% in 2006 to 59.5% in 2008 with an overall average co-quinolone resistance rate of 49.7% while that of *Proteus* spp ranges from 44.4% to 51.7%. But the highest co-quinolone resistances were observed with *Pseudomonas* with all the isolates showing resistance to multi-quinolones in 2007 and an overall average of co-quinolone resistance of 72.9%. These results may have supported the need for use of newer or other quinolones in the region.

General discussion

Numerous trials have demonstrated both the microbiological and clinical cure with the use of the fluoroquinolones in the treatment of Uncomplicated UTI in many regions (Gupta *et al.*, 2011). These advantages notwithstanding, the FQs antimicrobial agents are recommended by experts to be reserved or used as alternative in case of therapeutic failure to the first line agent or for complicated UTI and to preserve resistance development against them (Still and Norwood, 2012; UMMC, 2013).This approach seems justified since fluoroquinolone use is directly correlated with resistance development and hospital resistance is increasing (Still and Norwood, 2012). However the results obtained in this study is worrisome since high rates of resistances by these uropathogenic bacteria are observed with most of the fluoroquinolones currently in use in the region.

CONCLUSION

Except in some few isolated cases, the resistances offered by the trio of *Klebsiella, Proteus, and Pseudomonas* UTI isolates to the fluoroquinolone antimicrobial agents used in the region has far exceeded 20% and their empiric choices without microbiological laboratory assays may both constitute irrational drug therapy and at the same time risking therapeutic failure. It is therefore recommended that the introduction of newer FQs agents be made in the region while at the same time strengthening the local and national antibiotic policies.

REFERENCES

1. Azra SH, Nair D, Kaur J, Baweja G, Deb M, Aggarwal P. Resistance Patterns of Urinary Isolates in a Tertiary Indian Hospital J Ayub Med Coll Abbottabad 2007; 19(1): 39-41
2. Chang SC, Chen YC, Hsu LY. Epidemiologic study of pathogens causing nosocomial infections. J Formos Med Assoc 1990; 89:1023-30.
3. Curtis M. Urinary Tract Infection caused by *Klebsiella*.
4. http://www.ehow.com/about_5314991_urinary-infections-caused-klebsiella.html. 2013. Retrieved July 2013
5. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Dis Mon 2003; 49:53-70.
6. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America

and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011; 52(5):e103-20.

7. Hootan TM. Recurrent urinary tract infection in women. Int J Antimicrob Agents 2001; 17:259-68.
8. Iqbal J, Rahman M, Kabir MS, Rahman M. Increasing ciprofloxacin resistance among prevalent urinary tract bacterial isolates in Bangladesh. Jpn J Med Sci Biol. 1997; 50(6):241–250.
9. Jarvis WR, Martone WJ. Predominant pathogens in hospital infections. J Antimicrob Chemother 1992; 29:19-24.
10. Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. J Antimicrob Chemother. 2003; *51(1):69–76.*
11. Karlowsky JA, Philippe RS, Lagace´-Wiens, Patricia JS, Melanie RD, Heather JA, Andrew W, Daryl JH, George GZ. Antimicrobial Resistance in Urinary Tract Pathogens in Canada from 2007 to 2009: CANWARD Surveillance Study. Antimicrobial Agents And Chemotherapy, 2011; 55(7): 3169–3175
12. Leone M, Albanese J, Garnier F, Sapin C, Barrau K, Bimar MC, et al. Risk factors of nosocomial catheter-associated urinary tract infection in a polyvalent intensive care unit. Int Care Med 2003; 29:929—32.
13. Litwin MS, Saigal CS, Yano EM, Avila C, Geschwind SA, Hanley JM, et al. Urologic Diseases in America Project: analytical methods and principal findings. J Urol 2005;173:933-7.
14. Memon BA. Predominant and Common cause of Urinary tract infection(s) in Sukkur city RMJ. 2007; 32(2): 99-101
15. Muhammad N, Mussharaf AK, Sajid MQ. Antibiotic Susceptibility Pattern of Bacterial Pathogens Causing Urinary Tract Infection in a tertiary Hospital Ann. Pak. Inst. Med. Sci. 2010; 6(4): 214-218 214
16. Neal RC. Urinary Tract Infection (Urethritis, cystitis and pyelonephritis). http://www.atsu.edu/faculty/chamberlain/Website/lectures/lecture/uti.htm 2011
17. Podschun R, Ullmann U. *Klebsiella* spp. as Nosocomial Pathogens: Epidemiology, Taxonomy, Typing Methods, and Pathogenicity Factors.Clin Microbiol Rev. 1998; 11(4): 589–603.

18. Saleh AA, Ahmed SS, Ahmed M, Sattar ANI, Md-RA Miah. Changing trends in Uropathogens and their Antimicrobial sensitivity pattern Bangladesh. J Med Microbiol 2009; 03 (01): 9-12
19. Shao HF, Wang WP, Zhang XW, Li ZD. Distribution and resistance trends of pathogens from urinary tract infections and impact on management. Zhonghua Nan KeXue. 2003; (9):690-2, 696.
20. Stamm WE, Norrby SR**.** Urinary tract infections: disease panorama and challenges. J. Infect. Dis. 2001; 183(Suppl. 1)**:**S1–S4.
21. Still KL, Norwood DK. Uncomplicated Urinary Tract Infections: A focus on Women's Health. US Pharm. 2012; 37(9):56-60
22. Struble K. Proteus Infections. Emedcine.medscape.com/article/226434. 2013. Retrieved July 2013
23. UMMC (University of Maryland Medical Center). Urinary Tract Infection. Umm.edu/health/medical/reports/articles/urinary-tract-infection. 2013 Retrieved July 2013
24. Veesenmeyer JL, Hauser AR, Lisboa T, Rello J. *Pseudomonas aeruginosa* virulence and therapy: evolving translational strategies. Crit Care Med 2009; 37:1777-86.
25. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Clin Infect Dis.* 1999; 29:745-758.
26. Woods DE, Schaffer MS, Rabin HR, Campbell GD, Sokol PA. Phenotypic comparison of *Pseudomonas aeruginosa* strains isolated from a variety of clinical sites. J Clin Microbiol 1986; 24:260-4.
27. Zervos MJ, Hershberger E, Nicolau DP, et al. Relationship between fluoroquinolone use and changes in susceptibilities to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991-2000. *Clin Infect Dis.* 2003; 37:1643-1648
28. Zulianello L, Canard C, Kohler T, Caille D, Lacroix JS, Meda P. Rhamnolipids are virulence factors that promote early infiltration of primary human airway epithelia by *Pseudomonas aeruginosa*. Infect Immun 2006; 74:3134-47.