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Antibiogram of *Escherichia coli* Isolates from Community Acquired Urinary Tract Infection: Special Reference to Fluoroquinolones Resistance

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A B S T R A C T

Urinary tract infections are common bacterial infections that affect the urethra, bladder, ureter or the kidney. It is the second most common infectious presentation in community medical practice with a high rate of morbidity and financial cost. This infection has burden rate of 150 million cases are estimated per annum while around 8 million cases are attributed to UTI in the USA. The study was conducted in the department of Microbiology, GMCH, Udaipur (Rajasthan), India during the period of year 2014-2015 on 356 patients, clinically diagnosed as Community acquired UTI. 100 non-duplicate urinary isolates of Escherichia coli from patients with clinically evident UTI were included in the study. Samples were collected from the patients after obtaining an informed verbal consent. Method employed for collection of urine was Midstream clean catch technique. Institutional Ethical clearance was obtained before commencement of the study. All relevant laboratory records of every subject was systemically recorded in pre designed data sheet. In this study, age group of 46-55 years was predominantly affected, irrespective of gender. Out of 100 screened strains of *Escherichia coli*, 33 were found to be ESBL and 67 to be non EBBL producers. The most resistant drug in Urinary Pathogenic Escherichia coli (UPEC) isolates was Ciprofloxacin with resistance rate of 82%. No resistance was observed for Fosomysin. Nitrofurantoin was found to be most susceptible drug with sensitivity rate of 98%. Fosomysin and Nitrofurantoin was found to retain 100% sensitivity, against non ESBL producers. Out of 82 Ciprofloxacin-resistant isolates, Nalidixic acid was most resistant drug with 100% resistance rate. Conclusion: Both Fosomysin and Nitrofurantoin can be used as drug of choice for empirical treatment of community acquired UTI. Resistance to Ciprofloxacin should not be considered as marker for resistance to other Fluoroquinolone. Thus Fluoroquinolone should only be prescribed following culture and sensitivity testing but not for empirical therapy.

Introduction

Urinary Tract Infection is the second most common infectious presentation in community medical practice (Kyung-Hwa *et al*., 2014). It is one of the most commonly occurring medical problems, causing considerable morbidity and healthcare costs (Smita Sood *et al*., 2012).

Urinary tract infection (UTI), considered among the most common bacterial diseases that affect a large part of the world's population. Urinary tract infection is generally treated empirically by general practitioners, for which they need to be aware of the locally prevalent strains and their

sensitivity pattern. Over the last few decades the resistance pattern of urinary isolates has been showing dramatic changes all over the world (Kadri *et al*., 2004).

In the United States, UTI account for approximately seven million office visits to physicians each year and over one million hospitalizations annually are attributed to or complicated by UTI (Orenstein *et al*., 1999).

UTI is an inflammatory response of the ureothelium to bacterial invasion that is usually associated with bacteriuria and pyuria (Campbell-Walsh Urology 10th edition).

UTI is a broad term that describes microbial colonization of the urine and infection of the structures of the urinary tract – kidney, renal pelvis, ureters, bladder, and urethra, as well as adjacent structures such as the perinephric fascia, prostate, and epididymis (Kunin, 1997). UTI may be asymptomatic (subclinical infection) or symptomatic (disease). Thus, the term *UTI* encompasses a variety of clinical entities, including asymptomatic bacteriuria (ABU), cystitis, prostatitis and pyelonephritis (Harrison's Principles of Internal Medicine).

When chemotherapeutic agents used to treat UTI were introduced in the early twentieth century, they were relatively ineffective, and persistence of infection after 3 weeks of therapy was common. Nitrofurantoin, which became available in the 1950s, was the first tolerable and effective agent for the treatment of UTI. This study aims to find out antibiogram of *Escherichia coli* isolates from Community Acquired Urinary Tract Infection with special reference to fluoroquinolones resistance.

Materials and Methods

The study was conducted in the department of Microbiology, GMCH, Udaipur (Rajasthan), India during the period of 2014-2015.

100 non-duplicate urinary isolates of *Escherichia coli* from patients with clinically evident UTI were included in the study. Samples were collected from the patients after obtaining an informed verbal consent. Method employed for collection of urine was Midstream "clean catch" technique. Institutional Ethical clearance was obtained before commencement of the study. All relevant laboratory records of every subject was systemically recorded in pre designed data sheet.

Inclusion criteria

Outdoor patients of age 15-50 years of both the sexes with symptomatic UTI.

In patients who had UTI at the time of admission.

Exclusion criteria

Patient with history of hospital admission a week before their presentation in OPDs.

Patient with indwelling catheterization.

Patient on antibiotic therapy in past 5 days will be excluded.

Patient who is not willing to participate.

Collection of urine sample

The clean catch mid-stream technique was employed to collect urine samples.

For female patients

After proper positioning of thigh, patient was instructed to spread the labia with one hand and clean the periurethral area and the perineum with 2-3 gauze pads saturated with soapy water, using a forward-to-back motion, followed by a rinse with sterile saline or water. Then pass a small amount of urine into

toilet, and finally urinate into the wide mouthed container.

For male patient

After washing his hand, clean catch mid-stream urine will be collected with foreskin separated.

Urine sample was collected aseptically in a sterile wide mouthed container. Each sample was properly labeled with patient name, OPD number etc. the specimens were then transferred to the laboratory as quickly as possible, usually within 1 hour after collection.

The sample was inoculated on Sheep blood agar and MacConkey agar (Hi Media Laboratories, Mumbai, India). The inoculated plates were incubated aerobically at 37°c for 24 hours and 48 hours for negative cases. After completion of incubation, the inoculated culture plates were observed for the presence of any bacterial growth. Colony count was done to calculate the number of colony forming unit per ml of urine.

The urine cultures which yielded significant bacteriuria ($>10^5$ cfu/ml) was included for further analysis. Plates were observed for typical colony characteristics and organisms were identified on basis of their cultural and biochemical properties.

Results and Discussion

A total of 356 patients, clinically diagnosed as Community acquired UTI, were included in study. Bacterial culture of urine specimen, of these patients was performed. Among these 356, bacterial growth were 151 (42.42%), 201(56.46%) had no growth and 4 (1.12%) had mixed growth (Table 1). The culture positivity of UTI among the female were (52%) in Community acquired UTI. Culture positivity among the male were (48%). The predominant age group in case of Community acquired UTI was 46-55 (Table 2).

Table 3 shows the aerobic organism that was isolated in culture. Out of 151 isolates the overall prevalence of *E. coli* was found 66.23% (n=100) in positive sample of urine. *Escherichia coli* were the most prevalent organism. It was followed by Coagulase negative *Staphylococcus* 10.6 % (n=16), *Enterococcus* 9.9% (n=15), *Pseudomonas aeruginosa* 4.63% (n=7), *Klebsiella* 4% (n=6), *Candida* species 1.99% (n=3), *Proteus mirabilis* 1.99% (n=3) and Coagulase positive *Staphylococcus* 0.66% (n=1).

Out of 100 strains of *Escherichia coli* 33 strains were Extended Beta Lactamase Producer (ESBL Producer) and 67 were non-ESBL producers. It was detected in accordance to guideline of CLSI. It is a confirmatory test, done by using Ceftazidime (30mcg) and Ceftazidime/Clavulanic acid (30/10mcg) discs.

The most resistant drug in UPEC isolates was Ciprofloxacin with resistance rate of (82%) followed by Ampicillin (81%), Amoxycillin/ Clavulanic acid (78%), Cefazolin (77%), Cefuroxime (76%), Cefotaxime (76%), Ceftazidime (66%) and Cefixime (76%). Co-Trimoxazole resistance rate was found to be (63%). Piperacillin/Tazobactam, Meropenam, Amikacin Nitrofurantoin was found to be susceptible drug with sensitivity rate of 87%, 90%, 91% and 98% respectively. Fosomycin has maximum sensitivity rate of 100 % (Table 4).

The most resistant drug in ESBL producing *Escherichia coli* isolates was found Ampicillin (100%), Amoxycillin/Clavulanic acid (100%), Cefazolin (100%), Cefuroxime (100%), Cefotaxime (76%), Ceftazidime (100%) and Cefixime (100%). Ciprofloxacin

ressistance rate was found to be (100%). Co-Trimoxazole resistance rate was found to be (72.72%). Nitrofurantoin was found to be susceptible drug with 93.93% sensitivity rate. Fosomycin, Piperacillin/ Tazobactam, Meropenam, Amikacin all has maximum sensitivity rate of 100 % to ESBL producing *Escherichia coli* (Table 4).

The most resistant drug in non-ESBL producing *Escherichia coli* isolates was Ciprofloxacin with resistance rate of (73.13%). Resistance rate of Ampicillin was (71.64%), Amoxycillin/Clavulanic acid (67.16%), Cefazolin (65.67%), Cefuroxime (64.18%), Cefotaxime (64.18%), Cefixime (64.18%) and Ceftazidime (49.25%). Co-Trimoxazole resistance rate was found to be (58.2%). Amikacin, Meropenam, Piperacillin/Tazobactam was found to be susceptible drug with 86.57%, 85.1% and 80.6% sensitivity rate respectively. Fosomycin and Nitrofurantoin was highly sensitive antimicrobial agent with sensitivity rate of 100 % to non-ESBL producing *Escherichia coli* (Table 4).

Nalidixic acid is the most resistant drug, with resistant rate of 100%. Resistant rate of Prulifloxacin was 65.85%, Ofloxacin 68.29%, Levofloxacin 19.5% while that of Norfloxacin was only 8.53% (Table 5).

In the present study, 356 urine samples from clinical cases of community acquired UTI was processed, out of which 151 (42.42%) were culture positive. Four (1.12%) samples yielded growth of more than one bacterial isolate. No growth was observed in 201 (56.46%) samples. Similar to our findings, Biswas *et al.,* (2014) had reported 42.45% culture positivity from urine samples. In comparison to our yield; lower positivity rate of 36.68 % and 38% was reported by Mehta *et al.,* (2013) and Ritu *et al.,* (2009) respectively. In contrast to our findings,

higher culture positivity rate of 65% in community acquired UTI was reported by Indu Sharma *et al.*

This variation may be attributed to the media selection, technique of growth and local prevalence rate. Even the standard personal hygiene and education status may be responsible.

In the present study, 62% of culture positive samples were from female and 38% were from males. In studies carried by Smita Sood *et al.,* (2012) and Devanad Prakash *et al.,* (2013); both had reported higher prevalence of UTI in females 62.42% and 65% respectively, whereas 37.67% and 35% in males. It was mainly due to anatomic and physiological factors.

In the current study 42% subjects were in between the age group of 46-55 years, which is similar to the finding of Amarjit Singh Vij *et al.,* and Devanand Prakash *et al.,* (2013); followed by 26% subjects in between 36-45 years and 16% of 15-25 years age group. In contrast to our findings, studies conducted by Dash *et al.,* (2013) and Razak *et al.,* (2012) showed maximum incidence of UTI among younger patients of age group 20-40 years. This variation may be due to the geographical and demographics of the region.

In our findings, Gram-negative uropathogens constituted the major part of the isolates 76.82% (116/151). Gram-positive uropathogens constituted 23.18% (35/151) of the total isolates. Out of 76.82% of Gram negative isolates, *Escherichia coli* was contributed by (66.23%); *Pseudomonas aeruginosa* (4.63%), *Klebsiella species* (4%); *Proteus mirabilis* (1.99%). Among 23.18% of gram positive, Coagulase Negative *Staphylococci* species was contributed by (10.6%), *Enterococcus* species (9.9%) and Coagulase Positive *Staphylococci* (0.66%).

Among yeast isolates (1.99%) *Candida* species was isolated. *Escherichia coli* 66.23% (100/151) was found the most prevalent gram negative bacteria in the positive urine samples of UTI. Similarly, to our findings Amarjit Singh Vij *et al.,* (2013) reported with *E. coli* prevalence rate of 68.7% and Moges Tiruneh *et al.,* (2012) reported rate of 42.3%, Gupta *et al.,* (2001) in USA found 75% *E. coli*. A study done by Dyer *et al.,* (1998) showed that the proposition of *E. coli* in the current decade has risen significantly, it accounted for 69% of positive cultures in 1991, which increased to 75% in 1994 and 81% in 1997.

Table.1 Result of growth in culture

Growth result	Number of strains isolated		
	Male (%)	Female (%)	Total (%)
Bacterial growth	72 (39.78%)	79 (45.14%)	151 (42.22%)
No growth	108 (59.67%)	93 (53.14%)	201 (56.46%)
Mixed growth	1 (0.55%)	3 (1.72%)	04 (1.12%)
Total	**181 (100%)** **(50.84%)**	**175 (100%)** **(49.16%)**	**356 (100%)** **(100%)**

Table.2 Age and sex distribution of the culture positive urine samples

Age (years)	Male (%)	Female (%)	Total (%)
15-25	10 (13.89%)	14 (17.72%)	24 (15.89%)
26-35	12 (16.67%)	13 (16.46%)	25 (16.56%)
36-45	16 (22.22%)	22 (27.85%)	38 (25.16%)
46-55	34 (47.22%)	30 (37.97%)	64 (42.38%)
Total	**72 (100%)** **(47.69%)**	**79(100%)** **(52.32%)**	**151(100%)** **(100%)**

Table.3 Bacteriological profile of urine specimen

ORGANISM ISOLATED	Number of isolates		
	Male (%)	Female (%)	Total (%)
Escherichia coli	47(65.28%)	53 (67.09%)	100 (66.23%)
Coagulase Negative *Staphylococci* species	7 (9.72%)	9 (11.39%)	16 (10.6%)
Enterococcus species	7 (9.72%)	8 (10.13%)	15 (9.9%)
Pseudomonas aeruginosa	4 (5.56%)	3 (3.80%)	07 (4.63%)
Klebsiella species	4 (5.56%)	2 (2.53%)	06 (4.00%)
Candida species	2 (2.78%)	1 (1.27%)	03 (1.99%)
Proteus mirabilis	1 (1.39%)	2 (2.53%)	03 (1.99%)
Coagulase Positive *Staphylococci* species	Nil	1 (1.27%)	01 (0.66%)
TOTAL	**72 (100%)** **(47.69%)**	**79(100%)** **(52.32%)**	**151 (100%)** **(100%)**

Table.4 Antibiotic susceptibility of ESBL and non-ESBL *Escherichia coli* producers

Antibiotic	ESBL producers (n= 33)		Non-ESBL Producers (n = 67)		*Escherichia coli* Producers (n = 100)	
	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive
Ampicillin	33 (100%)	Nil	48 (71.64%)	19 (28.36%)	81	19
Amikacin	Nil	33 (100%)	9 (13.43%)	58 (86.57%)	9	91
Amoxycillin/Cla vulanic acid	33 (100%)	Nil	45 (67.16%)	22 (32.84%)	78	22
Co-Trimoxazole	24 (72.73%)	9 (27.27%)	39 (58.21%)	28 (41.79%)	63	37
Cefazolin	33	Nil	44 (65.67%)	23 (34.33%)	77	23
Cefuroxime	33 (100%)	Nil	43 (64.18%)	24 (35.82%)	76	24
Cefixime	33 (100%)	Nil	43 (64.18%)	24 (35.82%)	76	24
Cefotaxime	33 (100%)	Nil	43 (64.18%)	24 (35.82%)	76	24
Ceftazidime	33 (100%)	Nil	33 (49.25%)	34 (50.75%)	66	34
Fosfomycin	Nil	33 (100%)	Nil	67 (100.0%)	0	100
Piperacillin/Tazo bactam	Nil	33 (100%)	13 (19.40%)	54 (80.60%)	13	87
Nitrofurantoin	2 (6.06%)	31 (93.94%)	Nil	67 (100.05)	2	98
Meropenem	Nil	33 (100%)	10 (14.93%)	57 (85.07%)	10	90
Ciprofloxacin	33 (100%)	Nil	49 (73.13%)	18 (26.875)	82	18

Table.5 Fluoroquinolones susceptibilities for 82 ciprofloxacin resistant *Escherichia coli*

ANTIBIOTIC	RESISTANT	SENSITIVE
Nalidixic acid	82	0
Norfloxacin	7	75
Ofloxacin	56	26
Levofloxacin	16	66
Prulifloxacin	54	28

E. coli had been the predominant organism isolated and no significant change has occurred in this picture over the last couple of decades. The reason of highest rate of isolation of *E. coli* causing UTI is due to the fact that most of the bacterial organisms causing UTI originate from the faecal flora and among these facultative anaerobes, *E. coli* constitutes the major portion superimposed by various virulence factors that facilitate the ascent of bacteria from faecal flora, introitus or periurethral area, up the urethra into the bladder and less frequently allow the organisms to reach the kidneys to induce symptomatic inflammation (Dyer *et al*., 1997). In present study, the antibiogram of UPEC isolates were done using Clinical and Laboratory Standards Institute guidelines (CLSI 2012). Among 100 isolates of UPEC; the resistance pattern which was observed for Ciprofloxacin (82%), Ampicillin (81%), Amoxycillin/Clavulanic acid (78%), Cefazolin (77%), Cefuroxime (76%), Cefixime (76%), Cefotaxime (76%), Ceftazidime (66%), Co-Trimoxazole (63%), Piperacillin/Tazobactam (13%), Meropenam (10%), Amikacin (9%), Nitrofurantoin (2%), Fosfomycin (0%). Fosfomycin was also included in this study as it is recommended by IDSA guidelines for optimal treatment of CA-

UTI. No resistance was observed for this antimicrobial agent. In our study, isolates with higher resistance were observed towards Ampicillin (81%), Amoxycillin + Clavulinic acid (78%). Same result was found in study done by Smita Sood *et al.,* (2012), in which resistance rate to Ampicillin and Amoxycillin+Clavulinic acid were recorded (81.18%) and (80.69%) respectively. Our result correlates with a study done by Biswas *et al.,* (2014), in which resistance rate to Amoxycillin+Clavulinic acid was (84.17%). UPEC showed higher resistance to older urinary microbial agents, which indicates that increased consumption of a particular antibiotic, can be a pathway to its resistance. Findings of this study, thus suggest that empirical treatment with these drugs may lead to failure of treatment.

In present study, the resistance to trimethoprim-sulfamethoxazole was observed in 63% of isolates. Similarly to our findings Biswas *et al.,* (2014), Hena Rani *et al.,* (2011), reported resistance rate of 65% and 69% respectively. Our results were higher as compared to a study of Arsian *et al.,* (2005), where trimethoprim/sulfamethoxazole resistance was observed in 36% of the uncomplicated UTIs. Trimethoprim/ sulfamethoxazole was the recommended treatment of choice for uncomplicated UTI according to the Infectious Diseases Society of America (IDSA) guidelines 2010. The IDSA also recommended that if resistance to Trimethoprim/sulfamethoxazole is greater than 20%, it should not be considered for first-line empirical therapy, thus in our setting trimethoprim/sulfamethoxazole may not be recommended for empirical therapy in uncomplicated UTI's.

In our study resistance rate to meropenem was 10%. Carbapenems (Meropenem) used in our study was found to be the sensitive drug against the isolates. The sensitivity rate of carbapenems was 90%. Similar result was found with Mandal *et al.,* (2012) with resistance rate of 9.2% and Devanad Prakash *et al.,* (2015) with resistance rate of 4.55%. Carbapenems are drug of choice for ESBL producers, as these strains are frequently multidrug resistant. Due to their high cost, parentral administration and the emergence of metallobetalactamase, it should not be used in community acquired UTI. Thus it should be restricted for use in critical patients where admission is required.

Fosfomycin is another oral antibiotic which is commonly used for treatment of CA-UTI. In our study susceptibility to fosfomycin was 100%. Our result matches the study done by Asfia Sultan *et al.,* (2015) in Aligarh Muslim University, Aligarh. Fosfomycin is an age-old drug. Resistance rate to this antimicrobial drug is low and most frequently acquired by chromosomal mutations that do not spread easily. The other benefits of use of fosfomycin are its less cost, dosage friendly, and non-toxic, nonallergic.

Fluoroquinolones are preferred as initial agents for empiric therapy of UTI, especially in those areas where resistance to first line of agent (Cotrimoxazol and Aminopenicillins) is likely to be concern. This is because they have high bacteriological and clinical cure rates. The resistance rate of ciprofloxacin was 82% in our study. The result of this study correlates with Deshmukh *et al.,* (2014), Biswas *et al.,* (2014) and Smita Sood *et al.,* (2012) who reported resistance of 83.01%, 90% and 75% respectively. Our result was higher than study conducted by John David Ohieku *et al.,* (2013) in which the resistance rate for ciprofloxacin was only 42%. Fluoroquinolones are a relatively new class of synthetic antibiotics with potent bactericidal, broad spectrum activity against many clinically important pathogens which are responsible for variety of infections and thus

widely used. In past few years, fluoroquinolones have been prescribed more frequently for the treatment of UTI. This may have led to an increase in fluoroquinolones-resistant *E. coli* infections, which are difficult to treat (Goettsch *et al*.,). In present study Ciprofloxacin resistant strains were evaluated for other quinolones also.

Nalidixic acid is first generation fluoroquinolones. Maximum resistance was observed in it, with resistant rate of 100%. Nalidixic acid was the first clinically available quinolone. However, because of its pharmacokinetic properties and the emergence of resistant isolates, its clinical use has been abandoned. Another mechanism can be as this is an older urinary microbial agent, which indicates that increased consumption of this antibiotic can be a pathway to its resistance.

Among the fluoroquinolones; Ofloxacin, levofloxacin, norfloxacin and prulifloxacin all have excellent bioavailability and have higher urinary concentrations. Their penetration into prostatic and renal tissue is also excellent. In our study resistance towards Ofloxacin was 68.29%, Prulifloxacin was 65.85%, and Levofloxacin was 19.5%; while that of Norfloxacin was only 8.53%.

Similar finding was observed in the study of Sumera Sabir *et al.,* (2014) where resistance to ciprofloxacin was (54.2%) and that of norfloxacin (11.2%). High resistance was observed in Ofloxacin due to its same mechanism of action and same generation as that of Ciprofloxacin. Prulifloxacin was not active against most of ESBL-producing gram-negative bacilli. This observation was similar to the previous reports from other studies (Giannarini *et al*., 2009). Levofloxacin achieve very high urine concentrations for eradication of most of the organisms that cause UTIs. Among recently developed

fluoroquinolones, levofloxacin is widely used in clinical practice because of its established efficacy and safety (Wimer, 1998; Norby *et al*., 1998). Levofloxacin is less likely to select resistant strains compared with older quinolone (Drugeon, 1999). In our study, not much resistance was noted against Norfloxacin; it is due to the less use of this drug in past few years.

The increased prevalence of antimicrobial resistance among UPEC limits the therapeutic options considerably. Both Fosomysin and Nitrofurantoin can be used as drug of choice for empirical treatment of community acquired UTI. Resistance to Ciprofloxacin should not be considering as marker for resistance to other fluoroquinolone as ciprofloxacin- resistant isolates were sensitive to levofloxacin and norfloxacin. This increase in resistance of fluoroquinolone among urinary isolates of *Escherichia coli*, suggests that empirical therapy with fluoroquinolone often fails in patients with community UTI. This restricts its use as an empirical drug of choice in community acquired UTIs. Thus fluoroquinolone should only be prescribed following culture and sensitivity testing but not for empirical therapy.

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