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SHORT COMMUNICATIUON

INCIDENCE AND PATHOGENESIS OF URINARY TRACT INFECTION- BANGLADESH PERSPECTIVE

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ABSTRACT

Urinary Tract Infection (UTI) is the problem for the hospitalized patients as Nosocomial infection and threat for the healthy peoples. Most of the Gram negative organisms are responsible for UTI but some Gram positive bacteria also cause UTI which is more in female than male. In this study, twelve organisms were found that causing UTI. The most common bacteria among the isolates which cause UTI was *E. coli* (53.8%). Moreover, 51-60 age group females (14.5%) and 75.3% OPD patients were found to be more prone to UTI. Most effective antibiotics sensitive against *E. coli* were Meropenem, Amikacin, Nitrofurantoin and Piparacillin / Tazobactam.

Urinary tract infection (UTI) is an infection that affects any part of the urinary tract. Most infections involve the lower urinary tract - the bladder and the urethra. When it affects the lower urinary tract it is known as a simple cystitis (a bladder infection) [1]. Urinary tract infection (UTI) is the most common bacterial infection in humans [2]. They account for more 8.6 million physician visits (84% by women) and over 1 million hospital admissions in the United States each year [3-5]. Acute uncomplicated cystitis remains one of the most common indications for prescribing antimicrobials to otherwise healthy community-dwelling women and up to 50% of all women experience one episode by 32 years of age [6-7]. Even today, UTI is one of the most important causes of morbidity and mortality in the developing countries like Bangladesh. This may be attributed to lack of proper research, faulty diagnostic procedures, abuse of chemotherapeutic agents of the people and little or no preventive measures. The alarming phenomenon is

that UTI does not restrict itself to the urinary tract only rather it can spread. It has been observed that only a small number of serologically distinct strains are responsible for the infections caused by *E. coli*. It has been observed that the greater dominance of *E. coli* in outpatient population is serologically distinct strains responsible for the UTI [8]. UTIs are among the most common bacterial infections worldwide, as about 50% of women will experience at least one episode of UTI during their lifetime [9] and it is also one of the leading causes of antibiotic consumption [10] which represent about 40% of hospital acquired infections [11] with substantial financial implications and significant consequences to morbidity and mortality. Diabetes mellitus (DM) has long been considered to be a predisposing factor for urinary tract infection (UTI) [12] and the urinary tract is the principle site of the infection in diabetics with increased risk of complications of UTI [13]. Acute UTI occurs in many women each year, and the annual costs of caring for those women are invariably very high in Bangladesh. Approximately, 60% of all women experience at least one UTI within their lifetime and roughly 20–30% women suffer from repeated infections [14, 15]. Sexual activities of women have been considered as important risk factors for UTI infections and recurrences [16], and with as frequently early marriage occurs in the slum women in Bangladesh, UTI may be promoted. In post-menopausal women, UTI risk factors may also comprise urinary incontinence [17]. Bacterial virulence properties may affect the risk of recurrence of infection as well [18-19]. However, some are reported with increased rates in patients with urological disorders and following repetitive courses with antibiotic treatments [20]. Uropathogenic *E. coli* utilize a number of virulence factors to adherence the uroepithelial cells; however, the strains fit to a limited number of serogroups mainly to O1, O2, O4, O6, O7, O14, O15, O18, O22 and O75 [21-22]. Antimicrobial resistance among uropathogenic *E. coli* may be increased with temporal and geographic fluctuations which may introduce multidrug resistant *E. coli* into the community [23]. In recent years, an increased number of Extended-Spectrum-Beta-Lactamases (ESBL) producing pathogens have been observed in outpatient settings, especially related to urinary tract infections (UTI), narrowing the treatment option with antibiotics [24]. In addition to age, sex, marital and social status, other risk factors include nature and type of strains associated with UTI. For example, Shiga toxin-producing *E. coli* may contribute to hemolytic uremic syndrome, elevated white blood cell count and C-reactive protein levels in infected patients [25]. The main objectives of the present study are to determine the incidence of UTI, find out the pathogens that causes UTI (admitted patients and out patients) in the selected hospitals and to determine the sensitivity pattern of antibiotics of the organisms that causes UTIs.

The observational study on Gram positive and negative bacteria was carried out in a tertiary care hospital of Dhaka city. This hospital is situated at the centre of Dhaka city. Many critical patients are referred here from all over Bangladesh. The study population comprised of patients with UTI in the hospital of all admitted patients of Inpatient Department (IPD) and Outpatient Department (OPD). Following criteria

were used to select the respondents in this study:- Inclusion Criteria- OPD patients and IPD patients who have high temperature with lower abdomen pains with burning maturation of urine pass that will be treated as UTI; Sample Size- The total numbers of samples collected were 166 and The UTI was determined by the medical records and Microbiology laboratory culture reports. From the culture reports, the number of developed UTI by the pathogenic organisms was determined. The questionnaire and checklist has been prepared used for the data collection. The instruments were prepared keeping in view the research questions, objectives and variables of the research work. The Culture media used in present study were reagent grade, which are- Blood agar media, MacConkey agar media, Mueller Hinton agar media and broth. The antimicrobial agents used in present study were - F(300mcg)-Nitrofurantoin, TZP (100/10mcg)-Piparacillin / Tazobactam, MEM (10mcg)- Meropenem, AK (30mcg)-Amikacin, CN (120mcg)-Gentamicin, CIP (5mcg)-Ciprofloxacin, CRO^{3rd} (30mcg)- Ceftriaxone, FEP^{4th} (30mcg)-Cefepime, CFM^{3rd} (30mcg)-Cefixime, SXT(1.25/23.75mcg)-Trimethoprime / Sulfamethoxazole, AMC (30mcg)-Amoxicillin / Clavulanic Acid, CXM^{2nd} (30mcg)-Cefuroxime, PB (300unit)-Polymixin B, CT (25mcg)-Colistin, CAZ^{3rd} (30mcg)-Ceftazidime, ATM(30mcg)-Aztreonam, PIP (10mcg)-Piparacillin, LEV (5mcg)-Levofloxacin, TOB (10mcg)-Tobramycin, CAR (100mcg)-Carbenicillin, AMP (10mcg)-Ampicillin, P(100mcg)-Penicillin, VA (30mcg)-Vancomycin, LZD (30mcg)-Linezolid, MH (30mcg)-Mynocycline, RD (5mcg)-Rifampin, FOX (30mcg)- Cefoxitin, E (15mcg)-Erythromycin, DA (2mcg)-Clindamycin.

Determination of UTI was carried out by the surveillance protocol formulated by the hospital authority as follows. For the OPD and IPD patients by the doctors prescribes urine collected by the patients, then send to phlebotomy room and phlebotomist check the urine containers and send to the pathology lab for examinations. Every morning temperature charts along with IPD patient's identifications (ID) number, collected from every departments nurses stations by the nursing services and the temperature chart was sent to the infection control (IC) team that those are trained up on data collection. The team then entered the ID number of febrile patients that temperature >100^{o}C, into the computer to retrieve patients relevant information regarding infections. On the day of admission, screening was carried out by physical examination and reviewing the medical chart. The study population was followed up after the admission to see any evidence of infection. The study populations were kept under observation till a first event of infection or discharge without infection. Samples were collected in following manner: Urine was collected as 1st hour mid stream urine aseptically from the patients after 48h admission. Recommended amount of urine is 15ml. 10ml of urine has been centrifuged. The slide was prepared for the Gram stain that centrifuged & un-centrifuged. The pus cells are also observed under microscope by 40X object from the centrifuged urine. For urine culture the un-centrifuged urine of 20µl has been inoculated on the Blood agar media and MacConkey agar media. After the inoculation that plate has incubated to incubator at 37^{o}C for

48h. Data was collected from microbiology department surveillance form for each patient. Most of the common bacteria were identified by standard manual methods practiced in the hospital laboratory [26]. Selection of antibiotics for each group of bacteria were made as per recommendation made by Clinical and Laboratory Standards Institute (CLSI) 2010, guideline [27]. The organisms were isolated from the specimen by inoculation and culture on the Blood agar & MacConkey agar for Urine sample incubated in incubator at 37°C. The organisms were inoculated under a laminar airflow. Identification of the organisms was done by the colony morphology, Gram stain and standard biochemical tests. After the inoculation, the media plate was incubated at 37ºC for overnight at least 18h for the 1st day reading. At that time, pick from the colony for biochemical tests and sensitivity.

The biochemical tests were done by Triple Sugar Iron (TSI), Motility Indole Urea (MIU), Citrate test, Bile Esculin, Oxidase test and Coagulase test. For the sensitivity the Muellar Hinton agar were used for common bacteria, Blood agar were used for *Streptococcus* sp. 2nd day reading was done after 48h and report has been deliverd. Gram staining was done as described by fenoxer *et al.;* 1990. Triple Sugar Iron Agar (TSI) test was used for initial identification of Gram-negative bacilli, particularly members of the *Enterobacteriaceae* sp., Motility test medium was used for testing motility of the bacteria. Semisolid agar (0.5%) was used for this purpose, Indole production was tested for some bacteria, which has the ability to degrade tryptophan to indole. Indole production was detected by Kovae's reagent, Urease test was used for detecting *Klebsiella* sp., Citrate utilization test was used for differentiating the intestinal bacteria and other microorganisms on the basis of citrate utilization [25]. Sensitivity testing was done for three to five isolated colonies of similar appearance. Turbidity of the organism in the tube will be adjusted by adding more bacteria or more saline to a turbidity equivalent to that of one half of McFarland standard which approximately corresponds to 1.5x10 organism ml. within 15 minutes after standardization of inoculums, a sterile cotton swab immerse into the bacterial suspension [28]. Each plate will be examined after overnight incubator (16-18h) and diameter of the complete zones of inhibition will be measured in mm with the help of scale place on the under surface of the Petridish without opening the lid. Zones of inhibition will be measured in two directions at right angles to each other through the center of the disc and average of the two reading will be taken [29].

During this study, total of 2617 patients, including IPD and OPD of which 166 had UTI with a total UTI rate of 6.30%. From these total 184 organisms were isolated, of which Gram positive bacteria, fermenting and non-fermenting Gram negative rods were present. It has been observed among the total isolated organisms causing UTI, the highest rates was found in *E. coli* (53.8%) and lowest rates to be *Acinetobacter* sp., *Serratia* sp. and *Stenotrophomonas* sp. (0.5%). The others organisms moderate rates are *Klebsiella* sp. (14.2%), *Enterococcus* sp. (7.7%), *Staphylococcus* sp. (5.4%), *Pseudomonas* sp. (4.9%),

Streptococcus sp. (3.8%), *Candida* sp.(3.8%), *Proteus* sp. (3.3%) and *Citrobacter* sp. (1.6%). Some patients were infected by multiple organisms, so the organisms were found 184 from 166 samples of patients caused UTI (Table-1). In case of age range and gender of patients having UTI, age 0 to 10 male Childs were infected 5.4% and female Childs (6.6%), 11 to 20 of age female patients were (1.8%), age 21 to 30 male patients were (1.8%) and female patients (11.5%), age 31 to 40 males were (0.6%) and females (6.6%), 41 to 50 of age males were (4.9%) and females (6.0%), 51 to 60 of age males were (6%) and females (14.5%), 61 to 70 of age males (7.8%) and females (12.7%), age 71 to 80 males were (2.8%) and females (6.6%), 81 to 90 of age males (2.8%) and females (1.8%); and 91 to 100 of age male patients were (0.6%) (Figure 1 & 2). The UTI rates, based on 2617 patients, including OPD and IPD was (6.3%) of which males were (2%) and females were (4.3%). The UTI of two departments -OPD and IPD, these are (75.3%) in OPD and (24.7%) in IPD were found (Figure 3). Another reason of UTI is wipe from back to front after using the toilet. That's because the urethra-the tube that transports urine from the bladder to the outside of the body is located close to the anus. Bacteria from the large intestine, such as *E. coli*, are in the perfect position to escape the anus and invade the urethra. The most of the male patients infected in UTI due to the taking outside unhygienic food and unsafe water. The antibiotic sensitivity patterns of Gram positive bacteria, Gram negative bacteria, fermenting & non-fermenting gram negative rods were also studied (Figure 4 & Table 2). *Proteus* were highest 100% sensitive against Piperacillin / Tazobactam, Meropenem, Amikacin, Gentamicin, Cefepime. Ceftriaxone and Trimethoprime / Sulfamethoxazole (83.3%), Cefixime and Ciprofloxacin (66.7%) and lowest rates of sensitive were Levofloxacin (33.3%), Cefuroxime and Amoxicillin / Clavulanic acid (50%). *E. coli* was highest rates of sensitive Meropenem (96.1%), Amikacin (94.9%), Nitrofurantoin (85.9%), Piparacillin / Tazobactam (82.8%), Gentamicin (62.6%). On the other hand the lowest rates of sensitive were Colistin (7.5%), Polymixin B (5.1%), Cefuroxime and Amoxicillin / Clavulanic acid (26.3%), Ciprofloxacin (29.1%), Cefixime (32.3%), Ceftriaxone and Trimethoprime / Sulfamethoxazole (40.4%) and Cefepime (41.4%). *Enterococcus* was highest sensitive against Gentamicin, Vancomycin and Linezolid (85.7%), Ampicillin (78.6%) and Nitrofurantoin (71.4%). The lowest rate of sensitive Meropenem, Ceftriaxone and Cefixime (7.1%), Piparacillin /Tazobactam, Amikacin, Ciprofloxacin, Cefepime and Trimethoprime / Sulfamethoxazole (14.3%) and Penicillin (57.1%). *Citrobacter* were highest sensitive against Piparacillin / Tazobactam, Meropenem, Amikacin, Gentamicin, Ciprofloxacin, Ceftriaxone, Cefepime and Cefixime 100%, Amoxicillin / Clavulanic acid and Cefuroxime (66.7%) and the lowest rates of sensitive Trimethoprime / Sulfamethoxazole, Polymixin B and Colistin (33.3%). *Pseudomonas* sp. was highest rates of sensitive against Piparacillin / Tazobactam (100%) and Ceftazidime (77.8%). On the other hand lowest rates were Polymixin B (22.2%), Meropenem, Amikacin, Cefepime, Colistin & Aztreonam (55.6%), Gentamicin, Levofloxacin, Tobramicin and Cabenicillin

(44.4%), Ciprofloxacin and Piparacillin (11.1%). *Acinetobacter* were highest rates of sensitive against Piparacillin / Tazobactam, Meropenem, Amikacin, Gentamicin, Ciprofloxacin, Cefepime, Trimethoxazole / Sulfamethoxazole, Piparacillin, Levofloxacin, Tobramicin (100%). *Klebsiella* sp. were highest sensitive against Meropenem and Amikacin (92.3%), Piparacillin / Tazobactam and Gentamycin (84.6%), Ciprofloxacin, Ceftriaxone and Cefepime (65.4%), Cefixime (61.5%). The lowest rates were Amoxicillin / Clavulanic acid (57.7%), Cefuroxime (50%), Trimethoprime / Sulfamethoxazole (23.1%), Nitrofurantoin (19.2%), Colistin (15.4%) and Tetracycline (3.8%). *Serratia* sp. was highest rates of sensitive against Piparacillin / Tazobactam (100%), Meropenem (100%), Amikacin (100%), Gentamycin (100%) and Ciprofloxacin (100%). *Staphylococcus* sp. was highest rates of sensitive against Vancomycin and Linezolid (100%), Rifampin (90%), Gentmycin (80%), Nitrofurantoin and Ciprofloxacin (70%), Trimethoprime / Sulfamethoxazole (60%). Lowest rates were Cefuroxime and Cefoxitin (50%), Ampicillin (20%), Penicillin and Tetracycline (10%). *Streptococcus* sp. was highest rates of sensitive against Ceftriaxone, Penicillin, Vancomycin and Linezolid (100%), Ampicillin (85.7%). The lowest rates were Ciprofloxacin (42.9%), Clindamycin (57.1%) and Erythromycin (28.6%). *Stenotrophomonas* were highest rates of sensitive against Piparacillin / Tazobactam, Trimethoprime / Sulfamethoxazole, Ceftazidime, Levofloxacine, Mynocycline (100%),

UTI is a common disease in Bangladesh. In this present Research study, an attempt was made to explore the patterns of organisms responsible for Urinary Tract Infection in Tertiary care hospital of Dhaka city, Bangladesh. Effective management of patients suffering from bacterial UTIs commonly relays on the identification of type of organisms that caused the disease and selection of an effective antibiotic agent to the organism. Diagnosis of UTIs is a good example of the needs for close cooperation between the clinician and the microbiologist / Medical Laboratory Scientist. In this Research study, it was observed that the common infective Gram positive organisms, Gram negative organisms, Fermenting and non-fermenting Gram negative rods organisms were *Proteus* sp. (3.3%), *E. coli* (53.8%), *Enterococcus* sp. (7.7%), *Candida* sp. (3.8%), *Citrobacter* sp. (1.6%), *Pseudomonas* sp. (4.9%), *Acinetobacter* sp. (0.5%), *Klebsiella* sp. (14.2%), *Serratia* sp. (0.5%), *Staphylococcus* sp. (5.4%), *Streptococcus* sp. (3.8%), *Stenotrophomonas* sp. (0.5%). In this present study out of 2617 patient urine samples, (6.3%) patients were infected by UTI of which males were (2.0%) and females were (4.3%). In this present study, out of 2617 patient urine samples, (6.3%) patients were infected by UTI of which (2%) and (4.3%) were males and females, respectively. According to the age, maximum patients belong to 51 to 70 yrs (20.5%) and in case of gender, maximum patients were Females (68.1%); where it was observed that women are more prone to UTIs than men which may because of short urethra and are closer to anus. In this study, the total isolated organisms causing UTI of highest rates to be *E. coli* (53.8%) and lowest rates to be *Acinetobacter* sp. (0.5%), *Serratia* sp. (0.5%)

and *Stenotrophomonas* sp. (0.5%). The others organisms moderate rates are *Klebsiella* sp. (14.2%), *Enterococcus* sp. (7.7%), *Staphylococcus* sp. (5.4%), *Pseudomonas* sp. (4.9%), *Streptococcus* sp. (3.8%), *Candida* sp. (3.8%), *Proteus* sp. (3.3%) and *Citrobacter* sp. (1.6%). Some patients were infected by multiple organisms, so the organisms were found 184 from 166 samples of patients caused UTI. According to the departments, highest rates of UTIs were OPD (75.3%) and lowest rate of UTIs (24.7%). *Proteus* sp. was highest (100%) sensitive against Piperacillin / Tazobactam, Meropenem, Amikacin, Gentamicin, Cefepime. Ceftriaxone and Trimethoprime / Sulfamethoxazole (83.3%), Cefixime and Ciprofloxacin (66.7%) and lowest rates of sensitive was Levofloxacin (33.3%), Cefuroxime and Amoxicillin / Clavulanic acid (50%). *E. coli* was highest rates of sensitive Meropenem (96.1%), Amikacin (94.9%), Nitrofurantoin (85.9%), Piparacillin / Tazobactam (82.8%), Gentamicin (62.6%). On the other hand the lowest rates of sensitive were Colistin (7.5%), Polymixin B (5.1%), Cefuroxime and Amoxicillin / Clavulanic acid (26.3%), Ciprofloxacin (29.1%), Cefixime (32.3%), Ceftriaxone and Trimethoprime / Sulfamethoxazole (40.4%) and Cefepime (41.4%). *Enterococcus* was highest sensitive against Gentamicin, Vancomycin and Linezolid (85.7%), Ampicillin (78.6%) and Nitrofurantoin (71.4%). The lowest rate of sensitive Meropenem, Ceftriaxone and Cefixime (7.1%), Piparacillin / Tazobactam, Amikacin, Ciprofloxacin, Cefepime and Trimethoprime / Sulfamethoxazole (14.3%) and Penicillin (57.1%). *Citrobacter* were highest sensitive against Piparacillin / Tazobactam, Meropenem, Amikacin, Gentamicin, Ciprofloxacin, Ceftriaxone, Cefepime and Cefixime (100%), Amoxicillin / Clavulanic acid and Cefuroxime (66.7%). And the lowest rates of sensitive Trimethoprime / Sulfamethoxazole, Polymixin B and Colistin 33.3%. *Pseudomonas* were highest rates of sensitive against Piparacillin/Tazobactam (100%) and Ceftazidime (77.8%). On the other hand lowest rates were Polymixin B (22.2%), Meropenem, Amikacin, Cefepime, Colistin and Aztreonam (55.6%), Gentamicin, Levofloxacin, Tobramicin and Cabenicillin (44.4%), Ciprofloxacin and Piparacillin (11.1%). *Acinetobacter* sp. were highest rates of sensitive against Piparacillin / Tazobactam, Meropenem, Amikacin, Gentamicin, Ciprofloxacin, Cefepime, Trimethoxazole/Sulfamethoxazole, Piparacillin, Levofloxacin, Tobramicin (100%). *Klebsiella* sp. were highest sensitive against Meropenem and Amikacin (92.3%), Piparacillin / Tazobactam and Gentamycin (84.6%), Ciprofloxacin, Ceftriaxone and Cefepime (65.4%), Cefixime (61.5%). The lowest rates were Amoxicillin/Clavulanic acid (57.7%), Cefuroxime (50%), Trimethoprime / Sulfamethoxazole (23.1%), Nitrofurantoin (19.2%), Colistin (15.4%) and Tetracycline (3.8%). *Serratia* sp. were highest rates of sensitive against Piparacillin / Tazobactam (100%), Meropenem (100%), Amikacin (100%), Gentamycin (100%) and Ciprofloxacin 100%. *Staphylococcus* was highest rates of sensitive against Vancomycin and Linezolid (100%), Rifampin (90%), Gentmycin (80%), Nitrofurantoin and Ciprofloxacin (70%), Trimethoprime / Sulfamethoxazole (60%). Lowest rates were Cefuroxime and Cefoxitin (50%), Ampicillin 20%, Penicillin and Tetracycline 10%. *Streptococcus*

was highest rates of sensitive against Ceftriaxone, Penicillin, Vancomycin and Linezolid (100%), Ampicillin (85.7%). The lowest rates were Ciprofloxacin (42.9%), Clindamycin (57.1%) and Erythromycin (28.6%). *Stenotrophomonas* were highest rates of sensitive against Piparacillin/Tazobactam, Trimethoprime / Sulfamethoxazole, Ceftazidime, Levofloxacine, Mynocycline (100%).

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Table 1: Total Isolated Organisms (Notes: Some patients were infected by multiple organisms).

Organisms	Number of Organisms	Total (%)
Proteus sp.	6	3.3
E. coli	99	53.8
Enterococcus sp.	14	7.7
Candida sp.	7	3.8
Citrobacter sp.	3	1.6
Pseudomonas sp	9	4.9
Acinetobacter sp.	1	0.5
Klebsiella sp.	26	14.2
Serratia sp.	1	0.5
Staphylococcus sp.	10	5.4
Streptococcus sp.	7	3.8

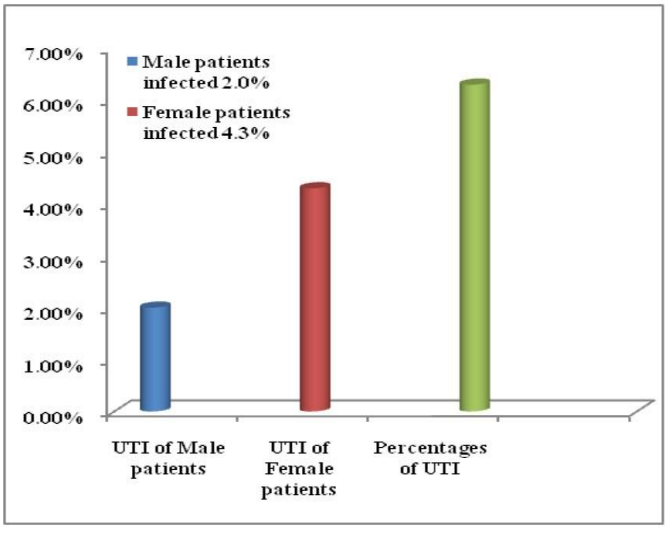

Figure 1: Gender distribution of studied samples.

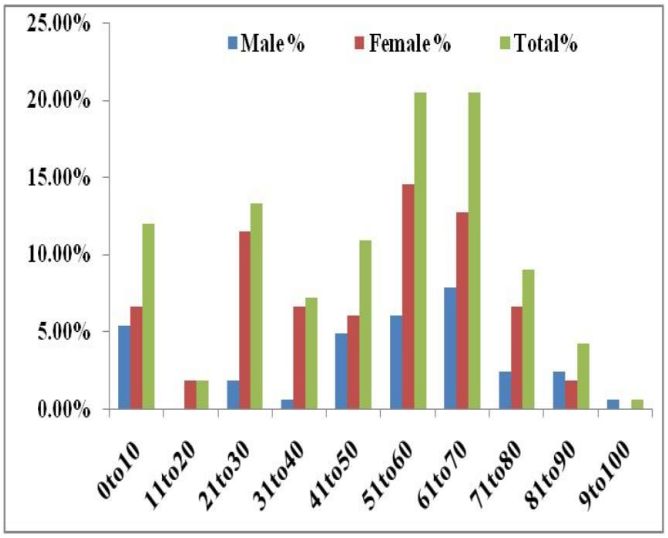

Figure 2: Age group distribution of studied samples

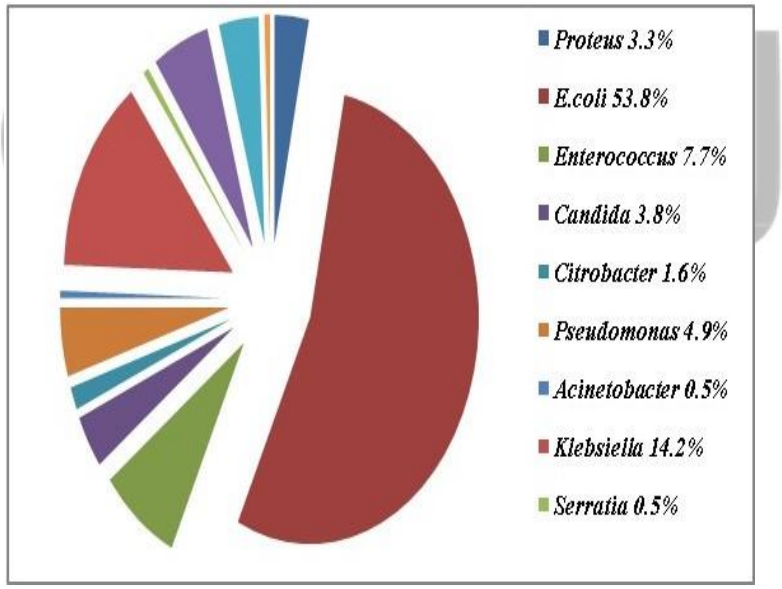

Figure 3: On the basis of departments of UTI cases.

Figure 4: Antibiotic sensitivity patterns of UTI causing bacteria.

Table 2: Bacterial antibiotic sensitivity pattern

Antibiotic	*Klebsiella sp.* (n-26); %	*Serratia sp.* (n-1) ; %	*Staphylococcus sp.* (n-10) ; %	*Streptococcus sp.* (n-7); %	*Stenotrophomonas sp.* (n-1) ; %
F (300mcg)	19.2%	-	70%	-	-
TZP (100/10mcg)	84.6%	100%	-	-	100%
MEM (10mcg)	92.3%	100%	-	-	-
AK (30mcg)	92.3%	100%	-	-	-
CN (120mcg)	84.6%	100%	80%	-	-
CIP (5mcg)	65.4%	100%	70%	42.9%	-
CRO^{3rd} (30mcg)	65.4%	-	-	100%	-
FEP^{4th} (30mcg)	65.4%	-	-	-	-
CFM^{3rd}(5mcg)	61.5%	-	-	-	-
SXT (1.25/23.75mcg)	23.1%	-	60%	-	100%
AMC (30mcg)	57.7%	-		-	-
CXM^{2nd} (30mcg)	50%	-	50%	-	-
PB (300unit)	-	-	-	-	-
CT (25mcg)	15.4%	-	-	-	-
CAZ^{3rd} (30mcg)	-	-	-	-	100%
LEV (5mcg)	-	-	-	-	100%
MH (30mcg)	-	-	-	-	100%
AMP (10mcg)	-	-	20%	85.7%	-
P (100mcg)	-	-	10%	100%	-
VA(30mcg)	-	-	100%	100%	-
LZD(30mcg)	-	-	100%	100%	-
TE(30mcg)	3.8%	-	10%	-	-
RD(5mcg)	-	-	90%	-	-
FOX(30mcg)	-	-	50%	-	-
E(15mcg)	-	-	-	28.6%	-
DA(2mcg)	-	-	-	57.1%	-