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Bacterial Pathogens in Urinary Tract Infection and Their Antibiotic Susceptibility Pattern

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Abstract **Objective**: Studies on prevalence of common bacterial pathogens causing UTIs in North India and their antibiotic susceptibility patterns against particular drugs. **Materials and methods:** A retrospective study conducted in UTI patients attending Dr Lal Path Labs, NRL, Delhi from March 2019 to December 2020. Clean catch midstream urine specimens collected for urine culture and sensitivity tests. Identification carried out by MALDI-TOF and antimicrobial susceptibility evaluated by VITEK® 2 with respective susceptibility cards (AST 280, 281, P628 Biomerieux, India) as per CLSI M100-S-30. **Results and Discussion**: In a period of 21 months observation, 65,619/2, 72,000 (24.1%) cases were positive to various clinical analyses of urine. Among them 40,568 (61.8%) were females and 25051(38.2%) were males. Female to male infection was 1.6:1. The age wise study of the culture positive cases indicates that the UTI infection occurs from infants (0 year) to elderly people (>=60 years). The 61.1% of the UTIs attributed by *E.coli* followed by *K. pneumoniae* (20.3%), *Enterococcus faecalis* (7.1%), *Pseudomonas aeruginosa* (5.4%), *Proteus mirabilis* (2.8%), *Enterobacter cloacae* (1.6%) *Acinetobacter baumannii* (1.1%) and *Staphylococcus aureus* (0.8%). Drug-sensitivity patterns suggest that the most susceptible antibiotic was Amikacin and Penems. However, penicillin derivatives, commonly prescribed advanced-generation cephalosporins, fluoroquinolones have found the most resistant drug among common uropathogens. **Conclusion:** Our study highlights the epidemiological trend of common bacterial pathogens causing UTIs and promotes information in order to establish the correct use of antibiotics. This study concluded that Gram-negative and Gram-positive uropathogens showed alarming rates of resistance for penicillin derivatives, advanced-generation cephalosporins, fluoroquinolones, and nitrofurantoin, while Amikacin, Penem group and Tigecycline seems the only suitable antimicrobials that could help clinicians in starting rational empirical antibiotic therapy.

Keywords: *Enterococcus species, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Escherichia coli, Uropathogens, Antimicrobial susceptibility*

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1. Introduction

Urinary-tract-infections (UTIs) are among the most common bacterial infections and major health/hygiene concern in the community with morbidity and comorbidities in patients with underlying conditions. In addition, it accounts for the majority of the reasons for hospital visits globally; accounting for as many as 35% of nosocomial infections and they are the second most common cause of bacteremia in hospitalized patients [1]. It is estimated that 150 million UTIs occur yearly worldwide, resulting in more than 6 billion dollars in direct healthcare cost [1,2].

UTI is common in women in the reproductive age and post-menopausal stage. The pregnant and young women in the age group 21-30 are more prone to UTI [3]. Diabetic mellitus prevalent in post-menopausal women has a link with UTI incidence. In the elderly aged male's diabetes and prostate problems enhance UTIs and elderly fatigue is common due to UTIs [1,3,4,5]. Of the different types of urinary tract infection, cystitis (lower urinary tract infection) and pyelonephritis (upper urinary tract infection) are the major problems [1,6]. For lower urinary tract infection, the common symptoms include inflammation and irritation in the lining of urethra and bladder, burning sensation or pain while urinating. More frequent urination and often with only a small amount of urine, sensation of having to urinate urgently, cloudy, bad smelling, or bloody urine, lower abdominal pain and mild fever. For upper urinary tract infections, the frequent symptoms include high fever, nausea and vomiting, shaking chills, pain in back or one side of waist [4]. The present study also reports children UTI in both genders. In the children fever, vomiting, loss of bladder control sleeping mode is common symptoms [7].

Recently UTI has become more complicated and difficult to treat because of the appearance of pathogens

resistant to the commonly used antimicrobial agents. The knowledge of etiology and antibiotic resistance patterns of the organisms causing urinary tract infection is essential. The main aim of the study was to determine the causative agents and antibiotic susceptibility pattern of UTI patients attending our lab. Urinary tract infection is one of the infectious diseases affecting both genders. The prevalence of drug resistance of uropathogens in urinary tract infected cases is a major problem to solve. With this background, the epidemiology of urinary tract infection was studied among the population of North India.

2. Material and Methods

A retrospective study conducted in 65,619 (24.1%) patients attending Dr Lal Path Labs, NRL, Delhi from March 2019 to December 2020 who had UTIs confirmed by positive urine culture reports were included in the study. In this study clean catch midstream urine collected and transported with Boric acid, sterile dry wide necked and leak proof containers were labeled with the date, name, time and serial number of the patient and the temperature of 2-4^{0}C with coolant pack to the laboratory. A calibrated loop method used for the isolation of bacterial pathogens from urinary samples. A sterile 4.0 mm platinum-wired calibrated loop was used which delivered 0.001 mL of urine. A loopful urine sample plated on 92 mm×16 mm polystyrene Petri dishes (Tarsons) containing selective and differential media CHROM agar orientation (France).

The inoculated plates incubated at 37°C for 24 hrs and those cultures that becomes negative at the end of 24 hours incubations were further incubate for 48 hours. After incubation, the urine culture were classified as negative, positive and contaminated when polymorphic bacterial growth (more bacterial species growth in one plate) was observed, the samples were classified as contaminated (exclusion criteria). The urine cultures were consider as negative when bacterial growth was lower than 103 cfu/ml (exclusion criteria). A specimen was considered positive for UTIs if an organism was cultured at a concentration of $\geq 10^5$ cfu/mL or when an organism was cultured at a concentration of 10^4 cfu/mL and >5 pus cells per high-power field were observed on microscopic examination of the urine (inclusion criteria). The crystals, casts and bacterial cells, parasites recorded. The physical parameters of collected urine specimens such as volume, pH, color, appearance was analyze and recorded. Bacterial identification was made using MALDI-TOF and antimicrobial susceptibility was evaluated by VITEK® 2 with respective susceptibility cards (AST 280, 281and P628 BioMerieux, India) as per as CLSI M100-S-30 [8].

The following antibiotics were used for the isolates, Ampicillin (AMP), Amoxycillin/clavulanic acid, Ticarcillin/Clavulanic Acid, Piperacillin/Tazobactam, Ciprofloxacin (CIP), Levofloxacin (LEV), Nalidixic acid (NAL), Tetracycline (TET), Amikacin (AMK), Gentamicin (GET), Ceftazidime (CTZ), Cefotaxime (CTX), Ceftriaxone (CFX), Cefepime, Cefoperazone sulbactam, Ertapenem, Doripenem, Imipenem (IMP), Meropenem (MRP), Nitrofurantoin (NTF), Trimethoprim/sulfamethoxazole (TM/SXT), Tigecycline, Vancomycin, Daptomycin and Teicoplanin. Standard strains of *E. coli* (ATCC 25922), *S. aureus* (ATCC 25923), and *P. aeruginosa* (ATCC 27853) were used routinely in this study as control.

The purpose of this study to summarized the most prevalent gram-negative and gram positive UTI pathogens such as *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Acinetobacter baumanii, Pseudomonas aeruginosa, Staphylococcus aureus* and *Enterococcus spp*. respectively and their antibiotic susceptibility with MIC using current diagnostic methods. The study will not cover the diagnosis of UTI in special patient populations, No data collected on the clinical background of the patients.

3. Statistical Analysis

The analysis done using the statistical software package Myla (Biomerieux). Age, gender, organisms causing UTI, their antibiotic sensitivity and resistance with MIC were included as variables in this study.

4. Results

The present retrospective study describes the distribution and antimicrobial susceptibility of bacterial species isolated from a large number of urinary samples collected over a 21 month period, as part of routine analyses, from unselected community patients (male and female of any age and clinical condition) living in the north India. The high number of available isolates allowed stratifying data according to patients' gender and age to evaluate the association of such variables to UTI etiology.

Significant bacteriuria detected in 65,619 (24.1%) out of 272,000 samples with Gram-negative bacteria (92.2%) were found in high prevalence than Gram positive (7.8%). Of the total 65,916 patients included, the age ranging from 1month to ≥61 years, 50.1% belonged to the elderly age group (>=56years). However, the prevalence was significantly higher in females than in males (females: 61.8%; males: 38.2%).

Among all the isolated bacterial uropathogens from UTI patients, *Escherichia coli* was found as the dominant bacteria with the prevalence rate of (61.1%), *Klebsiella pneumoniae* (20.3%) and *Enterococcus spp.* (7.1%), followed by *Pseudomonas aeruginosa* (5.4%), *Proteus mirabilis* (2.8%), *Enterobacter cloacae* (1.6%), *Acinetobacter baumanii* (1.1%) and *Staphylococcus aureus* (0.8%) (Figure 1).

The total prevalence of UTI in female patients was found to be 61.8% and in males about 38.2%. These results indicated that the prevalence of UTI was higher in female patients than in males. The highest susceptible age group of UTI patients irrespective of gender was found to be >56 years (50.1%) followed by ≤ 31-55 years (26.7%), 14-30 years (14.8%) and then between 0-13 years (7.5%) (Table 1).

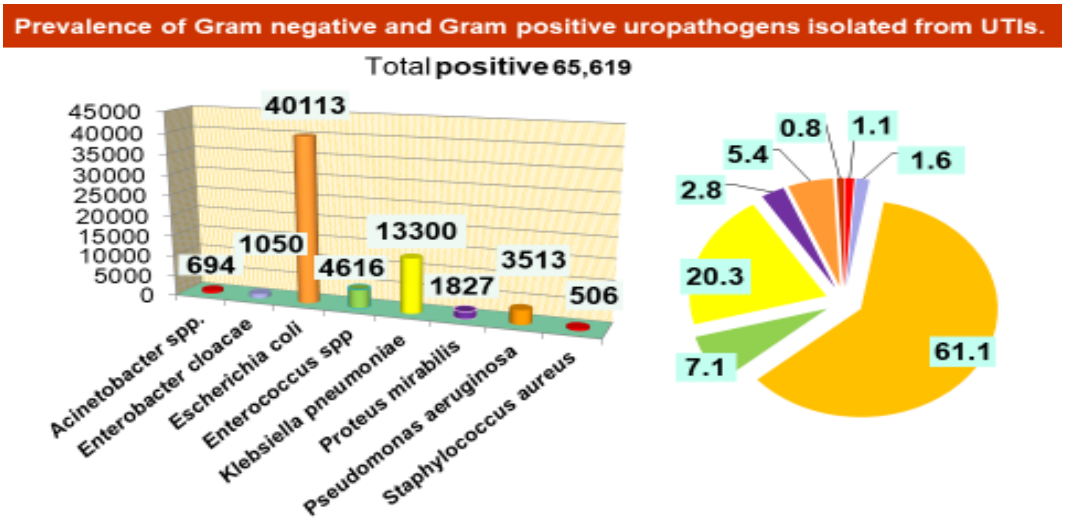

Figure 1. Distribution frequency of uropathogens isolated from UTIs

Table 1. Distribution of total UTI pathogens among different age groups in Delhi, India

Age groups	0-12	13-30	31-55	>=56
Uropathogens	4964 (7.5%)	9729 (14.8%)	17529 (26.7%)	33397 (50.9%)

Table 2. Prevalence rate and frequency distribution of UTI pathogens among different age groups in Delhi, India

Age groups / Organism	0-12	13-30	31-55	>=56
Escherichia coli	67.2	59.9	61.8	60.5
Enterobacter cloacae	1.6	2.2	1.6	1.4
Klebsiella pneumoniae	16.2	18.7	19.9	21.2
Proteus mirabilis	2	2.1	4.7	3.1
Acinetobacter baumannii	0.8	1.4	1.1	1.1
Pseudomonas aeruginosa	1.1	2.9	5.3	8
Enterococcus spp	5.9	10.6	8.1	5.6
Staphylococcus aureus	0.4	2.1	1	0.3

E. coli is the most frequently isolated predominant uropathogen in both the genders comprising all age groups (Table 2). Second predominant bacteria found to be *Klebsiella pneumoniae* whereas *Acinetobacter baumannii*, *Enterobacter cloacae*, *Enterococcus spp*. and *Staphylococcus aureus* were causing most infection in 13-30 age group in comparison to other age groups and >=56 years of age 8% patients were infected by *Pseudomonas aeruginosa.* It seems like pathogens *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are more specific to >=56 whereas 4.7% of *Proteus spp.* are specifically involved in 31-55 age group infection (Table 2).

Table 3. Antibiotic Susceptibility with Cumulative MIC of the antibiotics of various gram-negative uropathogens

Uropathogens		*Escherichia coli* N=40,113			*Klebsiella pneumonia* N=13,300		
Antibiotics	Range	S%	R%	MIC(µg/ml) 50/90	S%	R%	MIC(µg/ml) 50/90
Ampicillin	≤ 8 - ≥ 32	16.1	83.9	32/32	0.2	99.8	32/32
Amoxicillin/ clavulanic acid	≤ 8 - ≥ 32	51.2	48.8	8/32	48.1	51.9	16/32
Piperacillin/tazobactum	≤ 16 - ≥ 128	73	27	<=4/128	61.6	38.4	8/128
Cefuroxime	≤ 8 - ≥ 32	24.7	75.3	64/64	40.6	59.4	64/64
Cefuroxime/Axetil	≤ 4 - ≥ 32	21.7	78.3	64/64	38	62	64/64
Ceftriaxone	≤ 1 - ≥ 4	31.1	68.9	64/64	51.5	48.5	1/64
Cefoperazone/ sulbactam	≤ 16 - ≥ 64	82.1	17.9	<=8/64	68.9	31.1	<=8/64
Cefepime	≤ 2 - ≥ 16	54.4	45.6	2/64	64.1	35.9	1/64
Ertapenem	≤ 0.5 - ≥ 2	89.6	10.4	<=0.5/0.5	69.8	30.2	0.5/8
Imepenem	≤ 1 - ≥ 4	90.6	9.4	<=0.25/1	69.9	30.1	<=0.25/16
Meropenem	≤ 1 - ≥ 4	91.6	8.4	<=0.25/0.5	74	26	<=0.25/16
Amikacin	≤ 16 - ≥64	94.2	5.8	<=2/16	76.2	23.8	<=2/64
Gentamicin	≤ 4- ≥16	71.7	28.3	<=1/16	71.3	28.7	<=1/16
Ciprofloxacin	≤ 0.25 - ≥ 1	16.6	83.4	4/4	44.8	55.2	1/4
Nitrofurantoin	≤32 - ≥128	79.8	20.2	<=16/64	26.4	73.6	64/512
Trimethoprim/sulfamethoxazole	≤ 40 - ≥80	45	55	320/320	59.6	40.4	<=20/320
Tigecycline	≤ 0.5 - ≥2	99.3	0.7	<=0.5/0.5	77.5	22.5	<=0.5/2

Table 4. Antibiotic Susceptibility with Cumulative MIC of the antibiotics of gram-negative uropathogens

Uropathogens		*Enterobacter cloacae* N=1050			*Proteus mirabilis* N=1827		
Antibiotics	Range	S%	R%	MIC(µg/ml) 50/90	S%	R%	MIC(µg/ml 50/90
Ampicillin	≤ 8 - ≥ 32	****	****	****	26.7	73.3	(32/32)
Amoxicillin/clavulanic acid	≤ 8 - ≥ 32	****	****	****	52.7	47.3	(8/32)
Piperacillin/tazobactum	≤ 16 - ≥ 128	80.1	19.9	<=4/128	81.9	18.1	(<=4/8)
Cefuroxime	≤ 8 - ≥ 32	2.6	97.4	16/64	41	59	64/64
Cefuroxime/Axetil	≤ 4 - ≥ 32	1.3	98.7	16/64	39.4	60.6	64/64
Ceftriaxone	≤ 1 - ≥ 4	72.4	27.6	1/64	57.9	42.1	<=1/64
Cefoperazone/ sulbactam	≤ 16 - ≥ 64	85.8	14.2	<=8/64	78.6	21.4	<=8/32
Cefepime	≤ 2 - ≥ 16	84.4	15.6	1/8	65	35	1/64
Ertapenem	≤ 0.5 - ≥ 2	87.8	12.2	0.5/2	79.5	20.5	0.5/2
Imepenem	≤ 1 - ≥ 4	84	16	<=0.25/2	35.7	64.3	2/16
Meropenem	≤ 1 - ≥ 4	90.3	9.7	<=0.25/1	90.4	9.6	<=0.25/2
Amikacin	≤ 16 - ≥64	91.4	8.6	<=2/4	85	15	<=2/32
Gentamicin	≤ 4 - ≥16	87.6	12.4	<=1/16	61.3	38.7	<=1/16
Ciprofloxacin	≤ 0.25 - ≥1	71	29	<=0.25/4	23.9	76.1	1/4
Nitrofurantoin	≤ 16 - ≥128	46	54	64/128	*****	***	****
Trimethoprim/sulfamethoxazole	≤ 40 - ≥80	81.7	18.3	<=20/320	43.5	56.5	320/320
Tigecycline	≤ 0.5 - ≥2	93.5	6.5	1/2	****	****	****

Table 5. Antibiotic Susceptibility with Cumulative MIC of the antibiotics of Nonfermenter gram-negative uropathogens

Uropathogens		*Acinetobacter baumanii* N= 694			*Pseudomonas aeruginosa* N=3513		
Antibiotics	Range	Sensitive%	R%	MIC(µg/ml) 50/90	Sensitive%	R%	MIC(µg/ml) 50/90
Ticarcillin/ clavulanic acid	≤ 16 - ≥ 128	69.2	30.8	<=8/128	32	68	64/128
Piperacillin/tazobactum	≤ 16 - ≥ 128	70.1	29.9	<=4/128	57	43	16/128
Ceftazidime	≤ 16 - ≥ 64	68.7	31.3	4/64	60.3	39.7	4/64
Cefoperazone/ sulbactam	≤ 16 - ≥ 64	80.4	19.6	<=8/64	61.5	38.5	8/64
Cefepime	≤ 2 - ≥ 16	76.2	23.8	<=2/64	62.6	37.4	2/64
Doripenem	≤ 1 - ≥ 4	76.5	23.5	<=0.12/8	66.1	33.9	0.5/8
Imepenem	≤ 1 - ≥ 4	80	20	<=0.25/16	63.3	36.7	2/16
Meropenem	≤ 1 - ≥ 4	76.5	23.5	(<=0.25/16	63.4	36.6	1/16
Amikacin	≤ 16 - ≥64	71.4	28.6	<=2/64	65.8	34.2	4/64
Gentamicin	≤ 4 - ≥ 16	78	22	<=1/16	62.1	37.9	2/16
Ciprofloxacin	≤ 0.5 - ≥2	62.6	37.4	<=0.25/4	44.7	55.3	1/4
Minocyclin	≤ 4 - ≥ 16	81.7	18.3	<=1/16	****	***	****
Trimethoprim/sulfamethoxazole	≤ 20- ≥80	72.9	27.1	<=20/320	65.3	34.7	<=20/320
Tigecycline	≤ 0.5 - ≥2	87	13	<=0.5/4	****	****	****

Table 6. Antibiotic Susceptibility with Cumulative MIC of the antibiotics of Gram Positive uropathogens (in percentage)

Uropathogens		*Staphylococcus aureus* (N=506)			*Enterococcus species* (N= 4616)		
Antibiotics	Range	Sensitive %	R%	MIC(µg/ml) 50/90	Sensitive %	R%	MIC(µg/ml) 50/90
Benzylpenicillin	≤ 8 - ≥16	8.9	91.1	16/64	79.1	20.9	4/64
Oxacillin	≤ 2 - ≥4	52.5	47.5	2/4	***	***	***
Gentamicin	≤ 4 - ≥16	83.9	16.1	<=0.5/16	***	***	***
Ciprofloxacin	≤ 0.5 - ≥4	48.7	51.3	2/8	28	72	8/8
Levofloxacin	≤ 1 - ≥4	45.4	54.6	2/8	30.6	69.4	8/8
Linezolid	≤ 4- ≥8	88.8	11.2	2/8	84.2	15.8	2/8
Daptomycin	≤ 1- ≥8	100	0	0.25/1	***	****	***
Teicoplanin	≤ 8-≥32	90.4	9.6	2/4	81.9	18.1	<=0.5/32
Vancomycin	≤ 2-≥16	80.9	19.1	1/32	70.6	29.4	1/32
Tetracycline	≤ 4- ≥16	80.3	19.7	<=1/16	15.9	84.1	16/16
Tigecycline	≤ 0.5 - ≥2	100	0	<=0.12/0.5	***		***
Nitrofurantoin	≤ 16 - ≥64	94.9	5.1	<=16/32	79.2	20.8	<=16/128
Rifampicin	≤ 1- ≥4	83	17	<=0.03/4	***	***	***
Trimethoprim/sulfamethoxazole	<=40->=80	72.7	27.3	<=10/320	***	***	***

*** Not tested.

Selected antimicrobials included in this study possessed sensitivity and resistant patterns among different uropathogens.

Tested antibiotics against *E. coli*: Tigecycline found to be sensitive against 99% of the *E. coli* infected individuals followed by Amikacin and Penem groups having ≥ 90%sensitivity, Cefoperazone/sulbactam, Nitrofurantoin and Piperacillin/tazobactam sensitive against ≤ 80% whereas 50% of the *E.coli* infected individuals was sensitive to Amoxyclav with MIC 8µg/ml. The least sensitive and highly resistant drugs were Ampicillin, Cephalosporins, and Ciprofloxacin. Ninety percent of *Escherichia coli* isolates were tested against Ampicillin, and Cephalosporins having MIC 32µg/ml and 64µg/ml respectively. In this study *E. coli* were recorded with a high resistance rate (16.6%) against Ciprofloxacin activity (MIC50/90 4/4) demonstrating that 50 % and 90% of isolates were within 4µg/ml (Table 3).

Tested antibiotics against *K. pneumoniae*: Tigecycline and Amikacin found to be sensitive for >75% of the *Klebsiella* infected individuals. Cefoperazone/sulbactam, Penem groups and third and fourth generation Cephalosporins were sensitive against <70% of the infected individuals. TM/SXT were sensitive to 50% of the infected individuals and resistant to the remaining. Ampicillin were resistant to 99.8% demonstrated that 50% and 90% isolates were within 32µg/ml, of the infected individuals and Nitrofurantoin was resistant to 73.6% and sensitive for the 26.4% of the infected individuals. Second highest resistance recorded to Nitrofurantoin activity demonstrated that 50% of isolates were within 64µg/ml and 90% of isolates were within 512µg/ml.

Tested antibiotics against *Enterobacter cloacae*: Most of the drugs showed sensitive including Amikacin and Tigecycline found to be sensitive against ≥ 90% of the *Enterobacter* infected individuals followed by Penem groups having 90%sensitivity, whereas highly resistant drugs were cefuroxime (97.4%) and cefuroxime axetil (98.6%) demonstrated that 50% were within 16µg/ml and 90% isolates were within 64µg/ml, respectively. Second highest resistance recorded to Nitrofurantoin activity (MIC50/90 64/128) against *Enterobacter* demonstrated that 50 % of isolates were within 64µg/ml MIC and 90% isolates were within 128µg/ml in this study (Table 4).

Tested antibiotics against *Proteus mirabilis*: Ampicillin, Cefuroxime, Cefuroxime axetil, Nalidixic acid, Ciprofloxacin and Imepenem were least sensitive to the infected individuals (Table 4). Out of 1827 (2.8%) tested isolates of *Proteus mirabilis* 50% isolates having MIC 32µg/ml, 1µg/ml, 2µg/ml and 90% of isolates was having MIC 32µg/ml, 4µg/ml and 16µg/ml against Ampicillin, Ciprofloxacin and Imepenem respectively. Among the systemically active antimicrobial agents, Amikacin, Meropenem, Piperacillin/tazobactam and Cefoperazone/sulbactam appear to be the most active against this important pathogen.

Tested antibiotics against *Acinetobacter baumannii*: The best antimicrobials among non-fermenter gram-negative organisms were Tigecycline, Minocycline, Penems, and Cefoperazone/sulbactam and moderate resistance rate were Cefepime, Piperacillin/tazobactam and Gentamicin; however, the high resistance rate not found to be against any antibiotic (Table 5).

Tested antibiotics against *Pseudomonas aeruginosa:* Most of the drug among were showed moderate resistance including Penems, Ceftazidime, Cefoperazone/sulbactam, Cefepime, Piperacillin/tazobactam, Amikacin, Gentamicin and Trimethoprim/sulfamethoxazole. However, the Decreased susceptibilities was found to be against Ticarcillin/clavulanic acid (MIC at which 90% of isolates were inhibited [MIC (90), 128µg/ml] and Ciprofloxacin [MIC (90), 4 µg/ml] were noted (Table 5).

Tested antibiotics against *S. aureus*: Daptomycin and Tigecycline were sensitive to 100% of the infected individuals. Teicoplanin and Nitrofurantoin were sensitive to >=90% of the individuals. Gentamicin, Vancomycin, Tetracycline, Rifampicin were sensitive to >80 of the infected individuals. However, the highest resistance rate found to be against benzyl penicillin (R=91.1%) demonstrated that 50% and 90% of isolates were within 16µg/ml and 64µg/ml respectively. Decrease susceptibilities to Oxacillin (MIC at which 50% and 90% of isolates were inhibited [MIC (50), 2µg/ml] and [MIC (90), 4µg/ml] were recorded and quinolones (R=>60%) demonstrated that 50% were within 0.5µg/ml-1µg/ml and 90% of isolates were within >4µg/ml (Table 6).

Tested antibiotics against *Enterococcus species*: In this study, *Enterococci* carry a large number of resistance to Quinolones and Tetracycline, which were isolated from urine samples. Benzylpenicillin, Linezolid, Teicoplanin and Nitrofurantoin were sensitive to 80% of the infected individuals. Vancomycin were sensitive to 70% of the infected individuals and (MIC50/90 1/32) demonstrated that 50 % and 90% of isolates were within 1µg/ml and 32µg/ml respectively. Quinolones (MIC50/90 8/8) and Tetracycline activity (MIC50/90 16/16) recorded high resistance rate against *Enterococcus spp.* demonstrated that 50% and 90% of isolates were within 8µg/ml and 16µg/ml respectively (Table 6).

5. Discussion

Delhi is situated in Northern India and has extreme climatic conditions with high temperatures in summer and very cold in winters. For now, this study is a pioneer for this geographical area because of our huge data. This study may provide a valuable data on the present scenario of UTI infection and antimicrobial sensitivity pattern in Delhi (NCR) to improve efficient empirical treatment. Increasing antimicrobial resistance has been documented globally [1,6,9-18]. The prevalence of UTI was found to be 24.1% and this rate of prevalence is similar with the other studies which accounts for 25.6% [19], 32.2% [20], 32.6% [9], 35% [5], in India [21] respectively.

In this study, the Gram-negative bacilli such as *E.coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumanii, Proteus mirabilis* constituted 92.2% of the total bacterial isolates while Gram-positive isolates constituted 7.8%. Highest abundance and attribution of *E. coli* (60.1%) in UTI has been notice in our studies followed by *K. pneumoniae* (20.3 %), *Enterococci spp*. (7.1%), *Pseudomonas aeruginosa* (5.4%), *Proteus mirabilis* (2.8%), *Enterobacter cloacae* (1.6%), *Acinetobacter spp* (1.1%) and *Staphylococcus aureus* (0.8%). This result is consistent with reports from other

studies [12,13,16,17,21]. The studies on UTI in other places of the world also showed that *E. coli* and *Klebsiella pneumoniae* are the commonest uropathogens in UTI and *Klebsiella pneumoniae* was reported as the second most frequently isolated organism in UTI [7,9,13,17,21]. These findings were not correlate with other reports in which *P. aeruginosa* reported as the second most common bacterial isolate in UTI studies in India [22]. Our study showed a higher prevalence of UTI in females (61.8%) than in males (38.2%) which correlates with other findings, which revealed that the frequency of UTI is greater in females as compared to males [6,10,11]. This study shows that more females in the age group 21-30 than the reproductive or initial stage of married women are complaining of urinary tract problems. The reason behind this high prevalence of UTI in females is due to close proximity of the urethral meatus to the anus, shorter urethra, sexual intercourse, incontinence, and bad toilets [21].

The occurrence of UTI recorded high among the elderly (≥56 years, 50.1%) compared to middle-age patients (31-55 years, 26%) and young age patients (13-30 years, 17%; 0-13 years, 7%). In the present study also, observed that in both men and women UTI incidence increases over the age of 65 years. However, our results agree with the study done in other countries, which reported a trend of increasing complicated UTI reported in elderly patients [11,12].

The resistance to antibiotic drugs has been observed since its use and is an increasing worldwide problem. Here, we have described the impact of the antimicrobials with high resistant and sensitive rates against the uropathogens. The prevalence of multidrug-resistant *Enterobacteriaceae* increasingly reported in UTIs [9,13]. Most Common pathogens in UTIs have a high resistance to widely used antibiotics.

The alarmingly high resistance of Ampicillin and Amoxyclav to *E. coli* has been reported in studies from India and other countries [6,7,15,21,23]. The second most common urinary pathogen *Klebsiella* spp. presented even high resistance rates for the most commonly used antibiotic agents. The highest resistance observed for amoxicillin-clavulanic acid, which is similar to other findings [15,24]. Similarly, rates of *P. mirabilis* susceptibility to Ampicillin and Amoxicillin/clavulanate, were lower in this study (26.7% and 52.7%) in comparison to those described in previous reports where ranges of susceptibility rates of 53.6%–83.9% to Ampicillin, 79.6%–99.0% to Amoxicillin/clavulanate were reported [18]. Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were intrinsic resistant to Ampicillin and Amoxicillin clavulanic acid. These findings were correlated with other reports [9,13].

The alarming finding in this study is the resistance to advanced generation cephalosporin; the highest resistance seen against Cefuroxime/Axetil followed by Cefuroxime, Ceftriaxone, among all gram– negative uropathogens. In our study, Unfortunately, the increasing use of advanced generation cephalosporins has contributed to high level resistance amounting up to 60-70% was also concords with study done in Asia-Pacific countries [16] and also by other studies done in India [23,25]. A varying rate of prevalence (19–60%) of ESBL producing gram-negative bacteria has been reported from different studies across India [7,16]. It is of great concern that *E. coli* has developed a high rate of resistance against them as well, which is in line with other studies [13,15]. However, all Cephalosporins except Cefoperazone/sulbactam showed the highest resistance in the common urinary pathogens such as *E.coli, K. pneumoniae, Pseudomonas aeruginosa* and *P. mirabilis*; this high rate of resistance in uropathogens against Cephalosporins was also consistent with study done in India and other countries [7,9,13,23].

In recent years, the resistance rates for fluoroquinolones have risen exponentially. Tested fluoroquinolones in this study showed the least sensitive among uropathogens as in *E. coli*; CIP (S=16.6%): *K. pneumoniae*; CIP (S=44.8%), *Proteus mirabilis*; CIP (S=23.9%), *P. aeruginosa*; CIP (S=44.7%), and *S. aureus*; CIP (S=48.7%); *Enterococcus spp*. CIP (S=28%). Probably the most important finding in our study was the alarmingly high resistance to ciprofloxacin for *E. coli*. A recent data from 2020 for Romania, which also aimed to detect uropathogens involved in male UTIs, proved high resistance to *E. coli* to fluoroquinolones, similar to our findings [12].

In several studies, it has shown that all over the world the resistance rates are going up, especially for fluoroquinolones, due to over prescription. This reduces the clinical utility of fluoroquinolones [11,13,26]. In this study, the data show a statistically significant increase in resistance to ciprofloxacin for *Klebsiella* spp., *Proteus* and *P. aeruginosa*. This finding was also consistent with study in other countries and India [6,10,11,13,15,24,25]. Our findings about the fluoroquinolones did not correlate with others, which showed that they were highly effective (sensitive) [21,27,28].

The findings of this study showed that the resistance rates of most of the uropathogens to guideline-recommended antimicrobial agents were astonishingly high. However, in the study both carbapenems (Meropenem and Imepenem) were found to be the most sensitive drugs against isolated uropathogens. The sensitivity rate of carbapenems among uropathogens was as follows: *E.coli* (MRP; 91.6% and IMP; 90.6%), *Enterobacter spp.* (MRP; 90% and IMP; 84%), *Acinetobacter spp.* (MRP; 76.5% and IMP; 80%), *K. pneumoniae* (MRP; 74% and IMP; 69.9%), and *P.aeruginosa* (MRP; 63.3% and IMP; 63%), Similar findings were reported from other region [10,13,21,28].

However, *Proteus mirabilis* did not show a high susceptibility to IMP (35.7%) but it was susceptible to MRP (89.4%). *Proteus* spp. is a typical nosocomial pathogen that has been isolated particularly from patients with complicated UTIs. *Proteae* (a tribe including *Proteus*, *Morganella spp*. and *Providencia* spp.) are intrinsically resistant to nitrofurantoin, colistin, and have decreased susceptibility to Imipenem [15]. In our data, *Proteus mirabilis* retained susceptibility to Piperacillin/tazobactam, Amikacin, and Meropenems. Resistance rates for all other antibiotics make them unsuitable for empirical treatment of *Proteus*-caused UTIs.

Surprisingly, we detected relatively low resistance rates for uropathogens to Amikacin, and this last, “old forgotten drug,” are a good first-line, empiric treatment of choice,

the effectiveness of this antimicrobial agent on resistant strains, concluding that they are a valuable choice for uncomplicated lower UTIs. Moreover, *E. coli*, *K. pneumoniae*, and other gram-negative bacteria showed susceptibility against Amikacin, which is also as similar to a study by [9,10,13,27]. Our study was in line with another study where we observed that most tested bacteria were far more susceptible to amikacin than that toward gentamicin [15,28].

Nitrofurantoin, one of the oldest oral antibiotics, showed high sensitivity. It showed its effectiveness against 70–75% of the isolates obtained from OPD. This drug exhibited a low resistance rate in the major part of the world (0–5.4%) [19]. Despite its use for many years which was because of localized action of this drug only on the urinary tract. So, nitrofurantoin can be considered as first line, cost saving and effective oral therapy in UTI patients at OPD level [10]. In our previous paper [29], we emphasized the importance of the Nitrofurantoin status in determining the outcome of uropathogens infection. Our new data with the MICs of Nitrofurantoin that concluded Nitrofurantoin resistance to *Klebsiella pneumoniae* and *Enterobacter spp*. might not offer a clinical solution when other antimicrobial drugs fail. However, all gram-negative uropathogens except E. coli, its effectiveness is still questionable and in agreement with other studies [9,29].

In this study, we found resistance to Trimethoprim-sulfamethoxazole (TM/SXT) in gram-negative uropathogens such as *E.coli* and *Proteus* were 55% and gram-positive *S. aureus* were 28% respectively. This finding was also consistent with a study done in south India and other countries who reported a high rate of resistance against TM/SXT [6,9,10,21,26,28]. This is in contrast to other studies where resistance is comparatively high ranging from 80% [7].

In addition, the present study investigated gram-positive uropathogens and their antimicrobial susceptibility profile that is essential for management and prevention of these bacteria in any healthcare facility. *Enterococcus species* have emerged as an increasingly second to *Staphylococci*, a leading cause of nosocomial infections in the last decade that have become commonly resistant to many antimicrobial agents.

Our data showed that quinolones resistance rates were worrying and inefficient in the antibiotic treatment of UTIs caused by Gram-positive bacteria. Therefore, we concluded that these antibiotics were not suitable for treatment of *Enterococci* infections in Delhi. Similar data were obtained from a study conducted in Saudi by [9] and other countries [13]. Haddad et al., [28] who reported Ciprofloxacin, Levofloxacin and Tetracycline were sensitive to Gram-positive bacteria *Enterococcus*, detected the inverse results in a study. These findings indicate that the resistance rate of uropathogens causing UTIs varies among different countries and period to period even with in the same country.

However, emergence of Vancomycin resistant *Enterococcus* (VRE) from urine has made it difficult to treat serious *Enterococcus* infections. This resistance rate was the highest with an upward trend that might be due to using antibiotics without restriction, which were in agreement with other studies [1,14]. In contrast, Vancomycin were detected effective for treatment of *Enterococcus* in a study by Chibelean *et al* [12].

In this study *Staphylococcus. aureus had a* large number of resistance to penicillin, Quinolones and Tetracycline, which were in agreement with other studies [9,13]. However, Linezolid, Teicoplanin, Vancomycin, and Daptomycin could be the proper therapies for the Gram-positive isolates, in line with other reports worldwide [10,13, 26].

In addition, we found 94.9% of *S. aureus* were sensitive to Nitrofurantoin. In contrast, Enterococcus showed 20.8% resistance to Nitrofurantoin. This resistance pattern observed was similar to the study that was done in south India [21] and in contrast to study done in other countries [28].

In most cases of UTIs, empirical antibiotic treatment begins before the urine culture results. Therefore, misuse of antibiotic treatment increases antibiotic resistance among uropathogens. It reflects that these useful antibiotics are instantaneously losing their efficacy in the treatment of UTI. These findings were correlated with other reports [9,10,13]. Several studies highlight the need to use antibiotics properly, in order to overcome the antibiotic resistance problem. Amikacin and Carbapenem groups are routinely used for the treatment of UTIs. In order to preserve these effective antimicrobials, physicians must rely on routine urine culture and sensitivity tests, and treat the patients accordingly.

6. Conclusion

Our study highlights the epidemiological trend of common uropathogens causing UTIs and promotes information in order to establish the correct use of antibiotics. This study concluded that the Gram-negative and Gram-positive uropathogens showed alarming rates of resistance for demonstrated penicillin derivatives, commonly prescribed advanced-generation cephalosporins, fluoroquinolones, and nitrofurantoin, while Amikacin, Penem group and Tigecycline seems the only suitable antimicrobials that could help clinicians in starting rational empirical antibiotic therapy for uropathogens.

Ethical Approval

It is not applicable.

Conflicts of Interest

There are no conflicts of interest.

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