



# Antimicrobial susceptibility of uropathogens and prescribing patterns in hospital- and community-acquired urinary tract infections in a tertiary care hospital

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## ABSTRACT

Periodic surveillances on the prevalence and antimicrobial susceptibility of uropathogens are necessary as they vary with time and geography. This prospective study for 8 months included 331 and 335 patients with hospital-acquired and community-acquired urinary tract infections (HA-UTI and CA-UTI), respectively. The prevalence of Gram-negative bacilli was higher in both groups, with *Escherichia coli* being the most prevalent uropathogen in both groups. An alarming number of isolates with multiple drug resistance was observed in HA-UTI and CA-UTI (47% and 46.2%, respectively). The mean multiple antibiotic resistance index in both groups was >0.2. Prescribing patterns and percentage antimicrobial susceptibility antibiograms revealed high resistance to commonly prescribed antimicrobials like  $\beta$ -lactams and fluoroquinolones. Retrospective data of the preceding 2 years revealed a statistically significant reduction in antimicrobial sensitivity of *E. coli* and *Klebsiella* isolates to several antibiotics. Antibiotic resistance is a major threat to patient safety in the hospital and the community. Strengthening of antimicrobial stewardship strategies like continued antimicrobial susceptibility surveillance, framing empirical antimicrobial policies, and promoting rational prescription of antimicrobials is the need of the hour.

## INTRODUCTION

With the advent of the “golden era of antibiotics”, human life expectancy significantly increased by cure of previously fatal infections, but the emergence of antibiotic resistance has become a global concern as it has large clinical and financial burden and needs urgent action (Kaur *et al.*, 2016). Standard treatments become ineffective and infections persist due to antimicrobial resistance. In a global review on antimicrobial resistance, 700,000 annual deaths attributable to antibiotic-resistant infections were estimated and are likely to rise to about 10 million by 2050, if action is not taken to combat this condition whose effect is especially felt in countries

referred to as the BRIC (Brazil, Russia, India, China) and MINT (Mexico, Indonesia, Nigeria, Turkey) (Joseph *et al.*, 2017). In a developing country, like India, a high burden of resistant infections is of concern due to the high rate of poverty which constrains the access to more effective but more expensive antimicrobial agents.

Urinary tract infections (UTIs) are common in clinical practice and are responsible for a large proportion of antibiotic consumption in the hospital and the community. Rational antibiotic treatment of UTI is essential to keep antibiotic consumption low, so as to reduce the emergence of resistance in the hospital and the community (Frimodt, 2002). Hospital-acquired UTI (HA-UTI) and community-acquired UTI (CA-UTI) differ in etiology, antimicrobial resistance profile, and prognosis (Agaba *et al.*, 2017; Aguilar-Duran *et al.*, 2012). The prevalence and susceptibility of uropathogens vary with time, geography, and from one institution to another (Mukherjee *et al.*, 2013). All institutions should therefore have continuous antimicrobial surveillance of uropathogens and periodic hospital

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antibiograms prepared, since it not only helps clinicians to select appropriate empirical policies, but also to monitor resistance trends within an institution, thereby optimizing therapy.

This study aims to assess the antimicrobial susceptibility of uropathogens and prescribing pattern of antimicrobials in HA-UTI and CA-UTI and to identify any statistically significant reduction in antimicrobial sensitivity of common uropathogens during the preceding 2 years. The study assessed the prevalence of uropathogens, risk factors, and multiple drug resistance (MDR), and also calculated the multiple antibiotic resistance index (MARI).

## METHODOLOGY

### Study design, selection of patients, and clinical data acquisition

A single-center retrospective study was conducted in the outpatient clinics of the Department of General Medicine, Gynecology, Nephrology, and Urology for the assessment of CA-UTI, and the assessment of HA-UTI was conducted in all inpatients admitted to Amrita Institute of Medical Sciences and Research Center, a tertiary care teaching hospital in Kerala, India. This prospective study was conducted from September 2018 to April 2019. Retrospective data from September 2016 to August 2018 were collected during this period. HA-UTIs are those that are identified after 48 hours of admission to hospital and CA-UTIs are those contracted outside of a healthcare setting or an infection present on admission, prior to development of the symptoms (Agaba *et al.*, 2017; Aguilar-Duran *et al.*, 2012). The study population consisted of patients aged  $\geq 18$  years whose urine culture reports were positive with significant bacteriuria [a colony count of  $\geq 10^5$  colony forming units (CFU) of bacteria per cc of urine in non-catheterized patients and  $\geq 10^2$  CFU of bacteria per cc of urine in catheterized patients] and antibiotic susceptibility tests were carried out (Hooton, 1990; Hooton *et al.*, 2010). Patients presenting more than once during the study period were considered only during first visit. Data were collected from the hospital's digital information system and direct review of inpatient medical records using predesigned forms. The study (IEC-AIMS-2018-PHARM-171) was approved by the Institutional Ethics Committee and written informed consent was obtained from all study participants.

### Prospective data

The prospective study included 331 HA-UTI patients [62 from Intensive Care Units (ICUs) and 269 from wards] and 335 CA-UTI patients [general medicine (94), gynecology (39), nephrology (74), and urology (128)] and from them 370 and 351 isolates of uropathogens was obtained, respectively. Patient demographics, risk factors, and prevalence of uropathogens were assessed. Culture and sensitivity (C&S) reports were analyzed to identify MDR isolates (non-susceptibility to at least one agent in three or more antimicrobial categories) and MARI was calculated (Magiorakos *et al.*, 2012). MARI, a tool for health risk assessment, ascertains if isolates are from a region of high or low antibiotic usage. MARI value ranges from 0 to 1, and values  $>0.2$  indicates "high-risk" sources of antibiotic

resistance, wherein antibiotics are frequently used or misused. This indicates that large proportions of bacterial isolates have developed resistance through exposure to several antibiotics (Köves *et al.*, 2017). MARI is determined by dividing the number of antimicrobials to which a pathogen is resistant by the total number of antimicrobials to which it was exposed (Chacko *et al.*, 2017; Mitchell *et al.*, 2016). Percentage susceptibilities of isolated uropathogens to routinely tested antimicrobials were represented in cumulative hospital antibiograms and developed according to the Clinical Laboratory Standard Institute guidelines on Analysis and Presentation of Cumulative Antimicrobial Susceptibility Testing. Species with less than 10 isolates have not been included due to sample size limitations. Organisms with 10–30 isolates have been included but were interpreted with caution, as small numbers may bias group susceptibilities. Intermediate sensitivity has not been included. Antimicrobial prescriptions before and after receipt of C&S reports were assessed.

### Retrospective data

Data from C&S reports were collected to identify a statistically significant reduction in sensitivity to antibiotics in the preceding 2 years (September 2016 to August 2017 and September 2017 to August 2018) among common uropathogens (*Escherichia coli*, *Klebsiella* isolates, and *Pseudomonas aeruginosa*). Between September 2016 and August 2017, 233 *E. coli*, 270 *Klebsiella* isolates, and 102 *P. aeruginosa* isolates and between September 2017 and August 2018, 132 *E. coli*, 169 *Klebsiella* isolates, and 59 *P. aeruginosa* isolates were identified with significant bacteriuria from HA-UTI data. Between September 2016 and August 2017, 413 *E. coli*, 209 *Klebsiella* isolates, and 43 *P. aeruginosa* isolates and between September 2017 and August 2018, 267 *E. coli*, 127 *Klebsiella* isolates, and 43 *P. aeruginosa* isolates were identified with significant bacteriuria from CA-UTI data.

### Statistical analysis

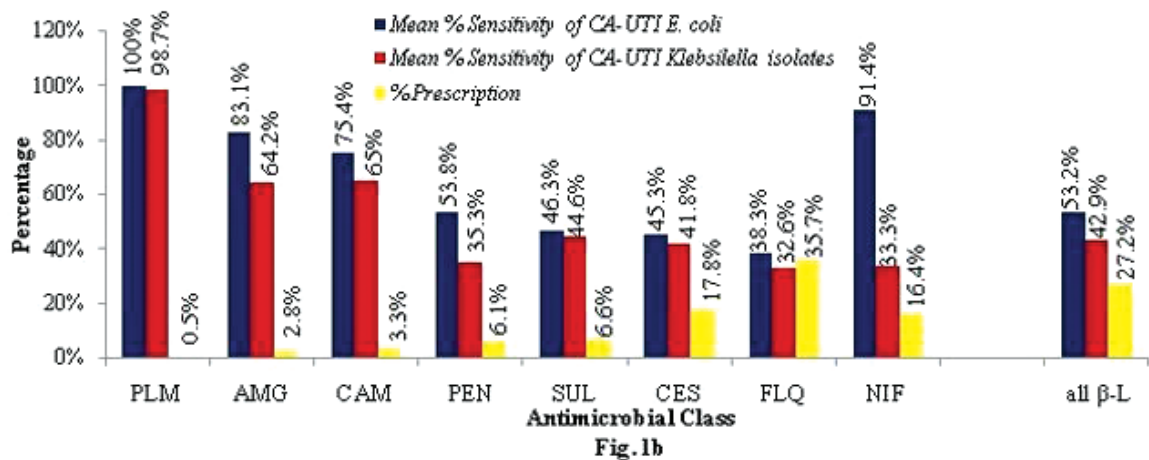
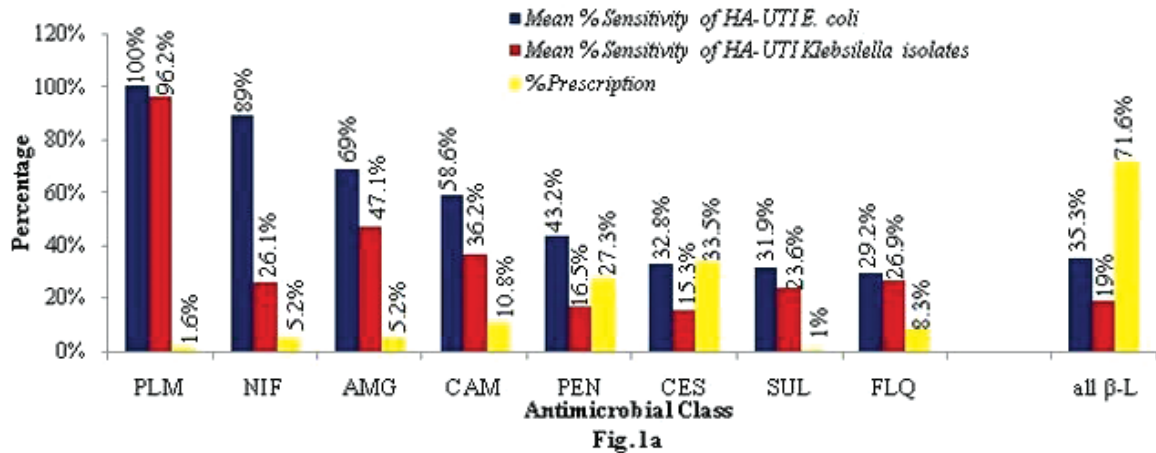
Data were compiled using Microsoft Excel and statistical analysis was conducted using IBM SPSS version 20. Descriptive statistical methods were used to calculate mean  $\pm$  standard deviation, median, and range for relevant parameters. Pearson's chi-square test was carried out in the retrospective study to determine whether the reduction in sensitivity to antibiotics observed between the preceding 2 years (September 2016–August 2017 and September 2017–August 2018) was statistically significant;  $p$ -values  $<0.05$  was taken as significant (Figs. 2 and 3).

## RESULTS AND DISCUSSION

### Prospective study

#### Demographics and risk factors

The HA-UTI study population consisted of 57.7% males and 42.3% females, with a mean age of  $61.96 \pm 15.51$  years (median age 65 years, range 18–91 years) and the CA-



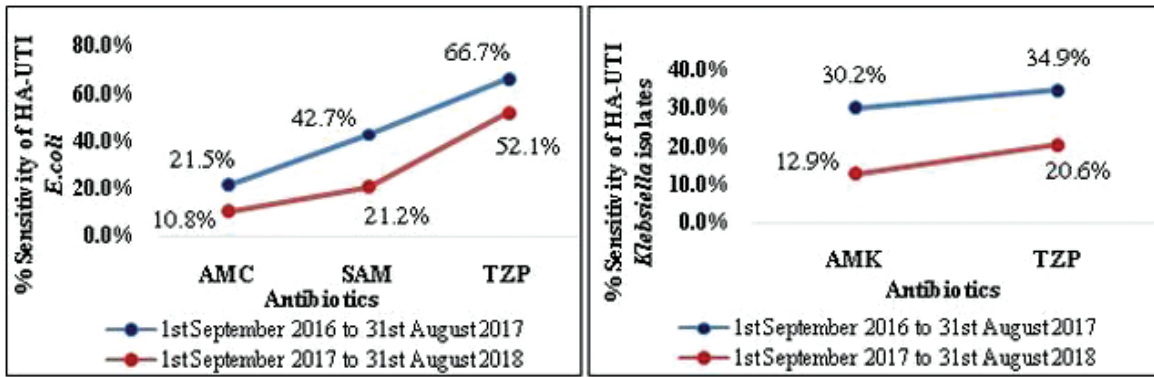
**Figure 1.** (a and b) Comparison of the mean percentage sensitivity (of most prevalent uropathogens in HA-UTI and CA-UTI, respectively) for an antimicrobial class with the percentage antibiotic prescription from that antimicrobial class. Increased prescription of antimicrobials was accompanied by decreased sensitivity to that antimicrobial class. PLM = polymixins; NIF = nitrofurans; AMG = aminoglycosides; CAM = carbapenems; PEN = penicillins; CES = cephalosporins; SUL = sulfonamides; FLQ = fluoroquinolones; all β-L = all β-Lactams.

UTI study population consisted of 53.4% females and 46.6% males, with a mean age of  $55.46 \pm 16.34$  years (median age 57 years, range 18–92 years). Females have a higher incidence of uncomplicated CA-UTI due to shorter and wider urethra and its proximity to the anus. Elderly patients (>50 years) are more likely to acquire UTI due to decreased immune function and increased number and duration of hospital admissions, similar to the study conducted by Karishetti and Shaik (2019). Females had a higher prevalence in the age groups <40 years in both HA-UTI and CA-UTI and >80 years in HA-UTI population. This is due to increased sexual activity and occurrence of pregnancies in lower age groups. Higher risk in post-menopausal women is due to alterations in bladder emptying and changes in vaginal flora with loss of estrogen and *Lactobacilli*. Males >40 years have a higher prevalence commonly due to an enlarged prostate, resultant ailments, and urogenital instrumentation; similar results were observed by Shevade and Agarwal (2013). Predisposing factors observed in the HA-UTI and CA-UTI study populations were diabetes mellitus (48% and 54.3%),

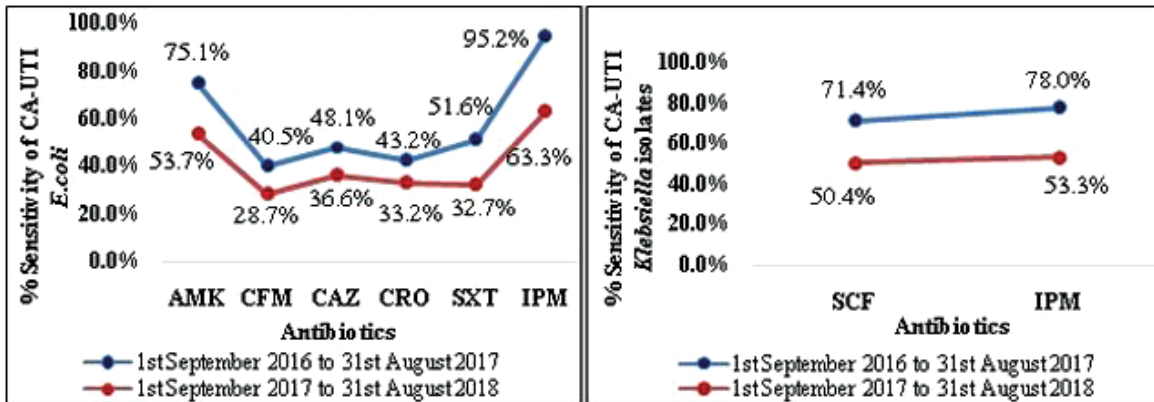
catheterization (51.1% and 12.8%), recurrent UTI (17.8% and 23%) benign prostatic hyperplasia (10.6% and 13.1%), pregnancy (0% and 4.5%), and other factors (such as urinary tract calculi and other kidney diseases, 45.3% and 27.5%, respectively). Catheterization was the major risk factor of HA-UTI in the study conducted by Melaku *et al.* (2012), where the risk of developing HA-UTI in catheterized patients was 2.6 times higher than non-catheterized patients. This can be due to increased use in inpatients, improper handling, and formation of biofilm. Diabetes mellitus often leads to UTI due to reduced immunity, diabetic nephropathy, peripheral neuropathy, and hyperglycemia that promote colonization in urinary tract. Diabetes mellitus was the major risk factor for CA-UTI, which is in accordance with Eshwarappa *et al.* (2011) and Chandrasekhar *et al.*'s (2018) studies.

#### Prevalence

Table 1 shows the prevalence of uropathogens in HA-UTI and CA-UTI. Among the 370 HA-UTI isolates, Gram-



**Figure 2.** Statistically significant ( $p < 0.05$ ) decrease in sensitivity of HA-UTI isolates between the preceding 2 years assessed using Pearson's chi-square test: *E. coli* to SAM = ampicillin/sulbactam ( $p = 0.001$ ); AMC = amoxicillin/clavulanate ( $p = 0.014$ ); and TZP = piperacillin/tazobactam ( $p = 0.009$ ), and *Klebsiella* isolates to AMK = amikacin ( $p = 0.001$ ) and TZP = piperacillin/tazobactam ( $p = 0.007$ ).



**Figure 3.** Statistically significant ( $p < 0.05$ ) decrease in sensitivity of CA-UTI isolates between the preceding 2 years assessed using Pearson's chi-square test: *E. coli* to AMK = amikacin ( $p = 0.001$ ); CFM = cefixime ( $p = 0.002$ ); CAZ = ceftazidime ( $p = 0.040$ ); CRO = ceftriaxone ( $p = 0.009$ ); SXT = cotrimoxazole ( $p = 0.022$ ); and IPM = imipenem ( $p = 0.001$ ), and *Klebsiella* isolates to SCF = cefoperazone/sulbactam ( $p = 0.001$ ) and IPM = imipenem ( $p = 0.001$ ).

negative bacilli (GNB) were the predominant cause of infection (68.6%), followed by Gram-positive cocci (GPC) (16.5%) and fungi (14.9%). *E. coli* was the most prevalent HA-UTI pathogen (19.7%), followed by *Klebsiella pneumoniae* (19.5%) and *P. aeruginosa* (14.3%). *Klebsiella* isolates (*K. pneumoniae* and other *Klebsiella* spp.) were seen in a total of 24.1% of isolates. The study conducted by Dharmishtha *et al.* (2012) and Kamat *et al.* (2009) also found *E. coli* to be the most prevalent HA-UTI uropathogen.

Among the 351 CA-UTI isolates, GNB was found in 89.7% isolates, followed by GPC (9.1%) and fungi (1.1%). *E. coli* was the most prevalent CA-UTI pathogen (53.6%), followed by *K. pneumoniae* (22.2%) and *Streptococcus* spp. (3.4%). *Klebsiella* isolates (*K. pneumoniae*, *Klebsiella oxytoca*, and other *Klebsiella* spp.) were seen in a total of 25.9% of isolates. Similar findings by Dharmishtha *et al.* (2012) showed *E. coli* to be the most prevalent CA-UTI uropathogen. Polymicrobial infections were seen in 9.4% and 4.8% of study patients with HA-UTI and CA-UTI, respectively, and were commonly among catheterized patients as long-term catheterization often leads to polymicrobial infections (Kamat *et al.*, 2009).

#### Multiple drug resistance and multiple antibiotic resistance index

MDR was identified in 47% and 46.2% of HA-UTI and CA-UTI isolates, respectively. Among the MDR isolates in each group, the highest was *Klebsiella* isolates (41.95%) followed by *E. coli* (27%) in HA-UTI and *E. coli* (52.5%) followed by *Klebsiella* isolates (35.8%) in CA-UTI. The alarmingly high number of MDR isolates is of major concern and is probably because majority of the patients are elderly and who are prone to repeated infections, leading to multiple exposures to antibiotics which indeed promotes resistance. The mean MARI for the MDR uropathogens was found to be  $>0.5$  in HA-UTI and  $\geq 0.2$  in CA-UTI. Thus, indicating that both hospital and community are "high-risk" sources of antibiotic resistance with frequent misuse or overuse of antibiotics. HA-UTI isolates have a higher mean MARI due to increased intensity of antimicrobial use in hospital and ineffective infection control, while in CA-UTI it indicates probable misuse of antimicrobials by over the counter dispensing of antibiotics, OP prescriptions for non-bacterial infections, self-medication, poor adherence to dosage



**Table 1.** Prevalence of uropathogens in HA-UTI and CA-UTI study participants.

Uropathogens	HA-UTI		CA-UTI			
	No.	%	No.	%		
Non-fermenter <i>Acinetobacter</i> spp.	9	2.4	3	0.85		
<i>Burkholderia cepacia</i>	1	0.27	–	–		
<i>C. koseri</i>	2	0.5	5	1.4		
<i>Citrobacter freundii</i>	1	0.27	1	0.28		
<i>Chryseobacterium indologenes</i>	4	1.1	–	–		
<i>E. coli</i>	73	19.7	188	53.6		
<i>Enterobacter</i> spp.	4	1.1	2	0.6		
<i>Enterobactercloacae</i> complex	–	–	2	0.6		
GNB	<i>K. pneumoniae</i>	72	19.5	78	22.2	
	<i>K. oxytoca</i>	–	–	2	0.6	
	<i>Klebsiella</i> spp.	17	4.6	11	3.1	
	<i>Morganella morganii</i>	2	0.5	–	–	
	<i>Myroides</i> spp	1	0.27	–	–	
	<i>Proteus mirabilis</i>	3	0.8	4	1.1	
	<i>Proteus vulgaris</i>	–	–	1	0.28	
	<i>Providencia rettgeri</i>	8	2.2	3	0.85	
	<i>P. aeruginosa</i>	53	14.3	11	3.1	
	<i>Serratia marcescens</i>	4	1.1	4	1.1	
	<i>E. faecalis</i>	14	3.8	6	1.7	
	<i>Enterococcus</i> spp.	33	8.9	5	1.4	
	GPC	<i>E. faecium</i>	10	2.7	–	–
		<i>Staphylococcus aureus</i>	2	0.5	7	2
		<i>Staphylococcus saprophyticus</i>	–	–	2	0.6
<i>Streptococcus</i> spp.		2	0.5	12	3.4	
<i>Candida glabrata</i>		–	–	1	0.28	
FUNGI	<i>Candida albicans</i>	14	3.8	–	–	
	<i>C. non-albicans</i>	21	5.7	1	0.28	
	<i>Candida guilliermondii</i>	1	0.27	–	–	
	<i>Candida</i> spp.	1	0.27	–	–	
	<i>Candida tropicalis</i>	18	4.9	2	0.6	
TOTAL	370	100	351	100		

regimens, antibiotic pollution, and overuse of antibiotics for other purposes, like in growth promoters for livestock. Hence, it is important to promote awareness regarding the rational use of antibiotics to the physicians, pharmacists, and patients. In the study conducted by Prakash and Saxena (2013), the MARI for HA-UTI ranged from 0.33 to 0.83 and for CA-UTI it ranged from 0.16 to 0.77. Table 2 gives the MDR, mean MARI, and MARI range of HA-UTI and CA-UTI study isolates.

#### *Antimicrobial susceptibility of uropathogens and prescribing pattern of antimicrobials*

Tables 3 and 4 represent the antibiograms of HA-UTI and CA-UTI isolates. In HA-UTI, *E. coli* had the highest sensitivity to drugs like colistin (CST), amikacin, meropenem (MEM), cefoperazone/sulbactam (SCF), and

piperacillin/tazobactam (TZP). *Klebsiella* isolates had the highest sensitivity to CST and amikacin. MEM, SCF, TZP, and nitrofurantoin showed <40% sensitivity to *Klebsiella* isolates. *Pseudomonas aeruginosa* showed 100% sensitivity to CST and <35% sensitivity to all other drugs. All GNB showed <30%–40% sensitivity toward common antibiotics like cefixime, ceftriaxone (CRO), amoxicillin/clavulanate, ciprofloxacin (CIP), and cotrimoxazole. Similar sensitivities were shown by *E. coli* in the study by Kamat *et al.* (2009). GPC showed a higher sensitivity to linezolid and vancomycin, while sensitivity to CIP was low. *Enterococcus* spp. and *Enterococcus faecium* had low sensitivity for ampicillin/amoxicillin and nitrofurantoin (NIT), while *Enterococcus faecalis* showed >60% for these drugs. Fungal HA-UTI isolates had 100% sensitivity to amphotericin B and fluconazole.

In CA-UTI, *E. coli* had the highest sensitivity to CST, MEM, amikacin, NIT, TZP, and SCF. Chandrasekhar *et al.* (2018) and Bardoloi and Babu (2017) suggested NIT as drug of choice for empirical treatment due to its higher sensitivity. *Klebsiella* isolates had the highest sensitivity to CST, MEM, and amikacin, whereas NIT sensitivity was only 33.3%. *P. aeruginosa* showed 100% sensitivity to CST and 50% sensitivity to TZP, while all other drugs had <45% sensitivity. Common antibiotics like cefixime, amoxicillin/clavulanate, CRO, CIP, and cotrimoxazole had <50% sensitivity to *E. coli* and *Klebsiella* isolates. *Streptococcus* spp. had high susceptibility to CRO, ofloxacin, vancomycin, linezolid, and ampicillin/amoxicillin. Only four fungal CA-UTI isolates were present, hence we did not include them in the antibiogram. The HA-UTI isolates had higher resistance than CA-UTI isolates.

A total of 57.7% of HA-UTI patients received empirical therapy, out of which 52.9% of the patients were resistant to the antimicrobial. After the C&S results, 77.6% of the participants received antimicrobials, out of which 34.6% of the patients received resistant empirical therapy and required a change in antibiotics. The most common empirical antibiotic was TZP, while the most common antibiotics prescribed after the C&S results were MEM and TZP. A common class of empirical antibiotics prescribed was cephalosporins (33.5%), followed by penicillins (27.3%) and carbapenems (10.8%). A common class of antibiotics used after the C&S results were penicillins (20.2%), followed by cephalosporins (19.4%) and carbapenems (16%). The change in percentage of common antibiotic class before and after the C&S results was because of high MDR isolates.

A total of 57.3% of CA-UTI patients received empirical antibiotics, out of which 47.9% of the patients were resistant to the agent due to increased use of  $\beta$ -lactams and fluoroquinolones with lower sensitivity. The commonly used empirical agent was NIT (16.4%), followed by levofloxacin (LVX) (14.6%) and cefixime (10.8%). Fluoroquinolones (35.7%) were the most commonly prescribed class of antimicrobials in empirical treatment of CA-UTI, followed by cephalosporins (17.8%) and nitrofurans (16.4%), which is similar to the study by Prakasam *et al.* (2012). After the C&S results, 60.6% of the study patients received antimicrobials, out of which 31.5% of the patients received resistant empirical

**Table 2.**MDR, mean MARI, and MARI range of HA-UTI and CA-UTI study isolates

Uropathogens	HA-UTI				CA-UTI			
	MDR Isolates (n = 174)		Mean MARI	MARI range	MDR Isolates (n = 162)		Mean MARI	MARI range
	No.	%			No.	%		
<i>Citrobacter koseri</i>	1	0.57	0.72	–	–	–	–	–
<i>C. freundii</i>	–	–	–	–	1	0.62	0.91	–
<i>Enterobacter</i> spp.	3	1.72	0.73	0.57-0.81	2	1.23	0.23	0.2-0.26
<i>Enterococcus</i> spp.	3	1.72	0.69	0.23-0.94	1	0.62	0.8	–
<i>E. coli</i>	47	27	0.63	0.18-0.93	85	52.5	0.57	0.23-0.94
<i>Klebsiella</i> isolates	73	41.95	0.86	0.49-1.0	58	35.8	0.73	0.11-0.94
<i>M. morganii</i> spp.	1	0.57	0.58	–	–	–	–	–
<i>Myroides</i> spp.	1	0.57	1	–	–	–	–	–
Non fermenter <i>Acinetobacter</i> spp.	5	2.9	0.79	0.52-0.93	1	0.62	0.86	–
<i>Proteus</i> spp.	1	0.57	0.68	–	2	1.23	0.4	0.37-0.43
<i>P. rettgeri</i>	9	5.2	1	–	2	1.23	0.83	0.7-0.95
<i>P. aeruginosa</i>	28	16.1	0.92	0.92-0.93	8	4.9	0.83	0.35-0.93
<i>S. marcescens</i>	2	1.15	0.83	0.78-0.89	1	0.62	0.28	–
<i>S. aureus</i>	–	–	–	–	1	0.62	0.38	–

**Table 3.** Percentage susceptibility (no. of isolates susceptible/total no. of isolates tested) of GNB from HA-UTI and CA-UTI isolates.

Uropathogens	<i>E. coli</i>		<i>Klebsiella</i> isolates <sup>a</sup>		<i>P. aeruginosa</i>	
	73	188	89	91	53	11
Total Isolates	HA-UTI	CA-UTI	HA-UTI	CA-UTI	HA-UTI	CA-UTI
Percentage susceptibility (no. of isolates susceptible / Total no. of isolates tested)						
AMK	79.2 (57/72)	92.1 (175/190)	51.7 (46/89)	67.4 (62/92)	30.2 (16/53)	36.4 (4/11)
SAM	62.5 (45/72)	72.5 (137/189)	25.8 (23/89)	45.1 (41/91)	0 (0/2)	–
AMC	34.4 (21/61)	32.9 (48/146)	24.3 (18/74)	30.1 (22/73)	0 (0/1)	–
FEP	16.7 (2/12)	41.4 (12/29)	8 (2/25)	31.3 (5/16)	28 (14/50)	40 (4/10)
CFM	23.6 (17/72)	30 (57/190)	12.2 (11/90)	38.5 (35/91)	–	–
CFP	29.2 (21/72)	37.8 (70/185)	13.6 (12/88)	40.7 (37/91)	29.2 (7/24)	40 (2/5)
SCF	66.2 (47/71)	87.9 (160/182)	26.9 (24/89)	55.4 (51/92)	30.8 (16/52)	18.18 (2/11)
CAZ	33.3 (8/24)	37.1 (33/89)	13.3 (4/30)	44.4 (20/45)	30.8 (16/52)	20 (2/10)
CRO	27.9 (19/68)	37.8 (65/172)	17.6 (15/85)	40.5 (34/84)	–	–
CIP	29.2 (21/72)	38.3 (72/188)	26.9 (24/89)	32.6 (30/92)	29.4 (15/51)	9.1 (1/11)
CST	100 (53/53)	100 (134/134)	96.2 (76/79)	98.7 (77/78)	100 (49/49)	100 (10/10)
SXT	31.9 (23/72)	46.3 (88/190)	23.6 (21/89)	44.6 (41/92)	0 (0/1)	–
GEN	58.8 (40/68)	74.1 (137/185)	42.5 (37/87)	60.9 (56/92)	30.6 (15/49)	27.3 (3/11)
IPM	41.7 (25/60)	57.1 (76/133)	33.8 (25/74)	54.8 (40/73)	17.1 (7/41)	10 (1/10)
LVX	50 (1/2)	–	0 (0/1)	0 (0/1)	28.8 (15/52)	9.1 (1/11)
MEM	75.4 (49/65)	93.6 (161/172)	38.6 (32/83)	75.3 (64/85)	28 (14/50)	36.4 (4/11)
NIT	89 (65/73)	91.4 (171/187)	26.1 (23/88)	33.3 (30/90)	0 (0/1)	–
PIP	14.3 (3/21)	22.4 (15/67)	4.3 (1/23)	25.8 (8/31)	30.8 (16/52)	36.4 (4/11)
TZP	66.2 (43/65)	89.1 (163/183)	24.4 (20/82)	51.2 (44/86)	34.7 (17/49)	50 (5/10)
TIM	38.6 (17/44)	52 (52/100)	3.8 (2/53)	24.5 (12/49)	26.7 (8/30)	0 (0/4)
TOB	–	–	–	100 (1/1)	30.8 (16/52)	27.3 (3/11)

AMK = amikacin; SAM = ampicillin/sulbactam; AMC = amoxicillin/clavulanic acid; FEP = cefepime; CFM = cefixime; CFP = cefoperazone; SCF = cefoperazone/sulbactam; CAZ = ceftazidime; CRO = ceftriaxone; CIP = ciprofloxacin; CST = colistin; SXT = sulfamethoxazole/trimethoprim; GEN = gentamicin; IPM = imipenem; LVX = levofloxacin; MEM = meropenem; NIT = nitrofurantoin; PIP = piperacillin; TZP = piperacillin/tazobactam; TIM = ticarcillin/clavulanic acid; TOB = tobramycin.

<sup>a</sup>*Klebsiella* isolates includes *K. pneumoniae* and other *Klebsiella* spp.

<sup>b</sup>Antimicrobial agents.

**Table 4.** Percentage susceptibility (no. of isolates susceptible/total no. of isolates tested) of GPC and fungi from HA-UTI and CA-UTI isolates.

Uropathogens	<i>Strepto-coccus</i> spp.	<i>Entero-coccus</i> spp.	<i>E. faecium</i>	<i>E. faecalis</i>	<i>C. non-albicans</i>	<i>C. albicans</i>	<i>C. tropicalis</i>	
Total Isolates	12	33	10	14	21	14	18	
	CA-UTI	HA-UTI	HA-UTI	HA-UTI	HA-UTI	HA-UTI	HA-UTI	
Percentage susceptibility (No. of isolates susceptible/total no. of isolates tested)								
Antimicrobial Agents <sup>a</sup>	AMP-AMX	100 (9/9)	3.2 (1/31)	0 (0/9)	69.2 (9/13)	–	–	–
	CRO	91.7 (11/12)	–	–	–	–	–	–
	CIP	100 (1/1)	0 (0/31)	0 (0/10)	21.4 (3/14)	–	–	–
	CLI	100 (6/6)	87.5 (14/16)	50 (1/2)	85.7 (6/7)	–	–	–
	LVX	–	87.5 (14/16)	20 (1/5)	85.7 (6/7)	–	–	–
	LZD	100 (7/7)	100 (31/31)	90 (9/10)	100(10/10)	–	–	–
	NIT	100 (6/6)	14.3 (5/35)	10 (1/10)	84.6(11/13)	–	–	–
	OFX	83.3 (10/12)	–	–	–	–	–	–
	PENG	90.9 (10/11)	2.9 (1/34)	0 (0/9)	61.5 (8/13)	–	–	–
	TEC	100 (7/7)	86.9 (20/23)	50 (3/6)	100 (8/8)	–	–	–
	TET	–	34.4 (11/32)	20 (2/10)	30.8 (4/13)	–	–	–
	VAN	100 (7/7)	90.3 (28/31)	70 (7/10)	100 (9/9)	–	–	–
	AMB	–	–	–	–	100 (21/21)	100 (14/14)	100 (18/18)
	FLC	–	–	–	–	100 (21/21)	100 (14/14)	100 (18/18)

AMP-AMX = ampicillin/amoxicillin; CRO = ceftriaxone; CIP = ciprofloxacin; CLI = clindamycin; LVX = levofloxacin; LZD = linezolid; NIT = nitrofurantoin; OFX = ofloxacin; PENG = penicillin G; TEC = teicoplanin; TET = tetracycline; VAN = vancomycin; AMB = amphotericin B; FLC = fluconazole.

<sup>a</sup>Antimicrobial agents.

therapy and required a change in antibiotics. Nitrofurans (25.5%) were the most prescribed class of antimicrobials after the C&S results, followed by fluoroquinolones (19.3%) and cephalosporins (16.9%).

Figure 1a and b shows the comparison of mean percentage sensitivity of most prevalent uropathogens with the percentage antibiotic prescription of an antimicrobial class. In both HA-UTI and CA-UTI, increased prescription of antimicrobials was accompanied by decreased sensitivity to that antimicrobial class. This is because increased use causes antibiotics to exert selective pressure which eventually leads to resistance. Low sensitivity leads to treatment failure, resulting in repeated exposures to multiple antibiotics, which further accelerates resistance. HA-UTI isolates had higher sensitive to reserve drugs like CST, vancomycin, and linezolid that are not frequently used in the hospital, while common agents, third generation cephalosporins and penicillins, had marked decrease in sensitivity. Carbapenem use for HA-UTI had increased due to an increase in MDR and hence reflected in the sensitivity to the drug, which has surprisingly decreased in *Klebsiella* isolates and *P. aeruginosa*. As seen in the graph, 71.6% of empirically prescribed antibiotics were  $\beta$ -lactams and hence had significant reduction in sensitivity for HA-UTI isolates. Oral agents, like CIP (fluoroquinolones), several cephalosporins, and cotrimoxazole, whose increasing resistance have been of concern for years worldwide had a marked decrease in sensitivity with only NIT maintaining higher sensitivity in both HA-UTI and CA-UTI. This has detrimental consequences on prophylaxis for

infections, like those after urological interventions, which place at risk the ability to treat common infections in community and hospital (Munoz-Davila, 2014).  $\beta$ -lactams like cefixime, LVX, and cotrimoxazole are widely prescribed for CA-UTI, while the global resistance rate of all uropathogens to CIP, cephalosporins, and penicillins is more than 50%, 35%–50%, and 50%, respectively (Cek *et al.*, 2014), thereby increasing the potential for resistance. NIT, despite being commonly prescribed in CA-UTI, has high sensitivity, probably due to its multiple mechanisms of action. A clinically significant correlation between antibiotic usage and resistance pattern was shown in the study conducted by Kamat *et al.* (2008), which is similar to our study where antibiotics frequently prescribed had a higher resistance than those prescribed less frequently.

### Retrospective study

Antibiotic susceptibility trends in HA-UTI isolates (Fig. 2) in the preceding 2 years showed a statistically significant decrease in sensitivity of (a) *E. coli* to ampicillin/sulbactam ( $p = 0.001$ ), amoxicillin/clavulanate ( $p = 0.014$ ), and TZP ( $p = 0.009$ ); and (b) *Klebsiella* isolates to amikacin ( $p = 0.001$ ) and TZP ( $p = 0.007$ ). *P. aeruginosa* sensitivity for antibiotics showed no statistically significant difference. The percentage of MDR isolates in both years was >50% of total isolates for *E. coli* and *P. aeruginosa*, while it was >75% of total isolates for *Klebsiella* isolates.

Figure 3 CA-UTI isolates showed a statistically significant decrease in sensitivity of (a) *E. coli* to amikacin ( $p =$

0.001), cefixime ( $p = 0.002$ ), ceftazidime (CAZ) ( $p = 0.040$ ), CRO ( $p = 0.009$ ), cotrimoxazole ( $p = 0.022$ ), and imipenem (IPM) ( $p = 0.001$ ); and (b) *Klebsiella* isolates to SCF ( $p = 0.001$ ) and IPM ( $p = 0.001$ ). *P. aeruginosa* sensitivity for antibiotics showed no statistically significant difference. The percentage of MDR isolates increased from 36.1% in the first year to 41.9% in the second year for *E. coli*, from 49.3% to 49.6% for *Klebsiella* isolates, and from 34.9% to 53.5% for *P. aeruginosa*.

Asia is known as the resistance epicenter due to its high prevalence rate of extended spectrum  $\beta$ -lactamase enzymes amongst *E. coli* and *Klebsiella* isolates, compared to North America and Europe (Jean *et al.*, 2016). A statistically significant reduction in sensitivity of antibiotics in our study is indicative of the increasing number of MDR strains and Extended Spectrum Beta-Lactamase (ESBL) producers among these isolates mainly due to overuse of these antibiotics. The emergence of resistance in UTI is of concern since majority of uropathogens are GNB (Mitchell *et al.*, 2016). Antimicrobial resistance, particularly the most common being *E. coli*, is directly associated with prescribing in primary care (Bhat and Sarkar, 2011). Resistance limits the options for treatment of various infections due to the decrease in development of new antibiotics.

Strengthening of antimicrobial stewardship strategies is the need of the hour. Empirical antimicrobial policies must be developed and regularly updated by continuous antimicrobial surveillance on prevalence and susceptibility of uropathogens since it varies with time and locality. Appropriate use of antimicrobials must be promoted through post-prescription reviews and feedback, antimicrobial utilization review programs, and auditing of dispensing practices. Monitoring antimicrobial usage, including indications, quantity, and pattern of use with restriction on use of carbapenems, fluoroquinolones, and third-generation cephalosporins is important. De-escalation from broad-spectrum antibiotics to narrower-spectrum antibiotics once the susceptibility data are available is essential. Reintroduction of old antimicrobials, like fosfomycin, is seen which is a potential old drug now used for the treatment of drug-resistant UTI and studies has shown promising results (Patwardhan and Singh, 2017; Prakash *et al.*, 2009; Pullukcu *et al.*, 2007). Effective infection control strategies and educating prescribers, dispensers, patients, and the general community on the appropriate use of antimicrobials is necessary.

Such measures will avoid overuse of broad-spectrum antibiotics and monitors resistance trends within an institution, thus optimizing treatment and improving rational prescription and use of antimicrobials. The overall goal should be to reduce the total consumption of antimicrobials and alter its usage in favor of regimens less likely to promote the emergence of resistant strains.

## CONCLUSION

*E. coli* was the most prevalent uropathogen in both HA-UTI and CA-UTI. Study patients in both groups showed alarmingly high MDR isolates with mean MARI value of  $>0.2$ . Percentage susceptibility of common uropathogens to frequently prescribed antimicrobials was low. Statistically significant reduction in antimicrobial sensitivity to commonly prescribed agents in the

past years indicates irrational use of antimicrobials. The need of the hour is to strengthen antimicrobial stewardship strategies, conduct continuous institutional surveillance on prevalence and susceptibility of uropathogens, and promote rational prescription and use of antimicrobials.

## AUTHORS' CONTRIBUTIONS

Achukutty Tomy, Aravind H, Emil David, and Ravina Ravi: conceptualization, investigation, formal analysis, visualization, and writing (original draft). Lakshmi R and Appu Thomas: supervision and writing (review and editing).

## CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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