



Research Article

Changing Patterns of Antimicrobial Susceptibility of Uro-pathogens in Community-acquired Urinary Tract Infections in Central India: Two Year Prospective Surveillance Report

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Abstract

Introduction: Antimicrobial resistance (AMR) is a global health crisis. Urinary tract Infection (UTI) are one of the most commonly encountered infections and its management is becoming increasingly difficult in view of AMR. The present study was conducted to determine the epidemiology of causative agents and their susceptibility antibiogram. **Methods:** The study was a prospective longitudinal study of UTI patients from 2020 to 2021 at AIIMS Bhopal, India. Patients presenting to outpatient department (OPD) or hospitalized to low priority area (LPA) like general ward or high priority area (HPA) like Intensive Care Unit (ICU) or High Dependency Unit (HDU) with symptoms of UTI and whose urine sample was sent for microbiological culture sensitivity test were included in the study. Urine samples were collected and processed in the department of microbiology using standard protocols. Antimicrobial susceptibility test was carried out using the Kirby-Bauer disc diffusion method as per the Clinical Laboratory Standards Institute (CLSI) guidelines on Muller Hinton agar. Samples growing more than two organisms were discarded as contaminant. Urine samples were collected and analyzed using standard protocols. **Results:** Out of 14526 patients of symptomatic UTI cases (58.0% from OPD, 35.9% from LPA and 6.0% from HPA), whose urine sample was sent for microbiological culture sensitivity test, 2222 (15.2%) showed positive growth. Among the 2222 number of positive growth, 1510 (67.9%) were community acquired, 186 (8.3%) was Health care Associated UTI and 526 (23.6%) cases could not be differentiated into either group. Among 1510 community acquired UTI cases, Gram Negative Bacilli (GNB) were identified in 88.7%, Gram Positive Cocci (GPC) in 10.1% and *Candida* in 1.0% cases. Among 1510 community acquired UTI cases, *E. coli* were identified in 58.9%, *K. pneumonia* in 15.4%, *Enterococcus* in 8.5% and *P. aeruginosa* in 4.2% cases. Among the *E. coli* isolates 3rd generation cephalosporin resistance was identified in 84% in OPD vs. 92% in LPA vs. 100% in HPA, fluoroquinolone resistance was in 82% in OPD vs. 94% in LPA vs. 100% in HPA, piperacillin resistance in 38% in OPD vs. 63% in LPA vs. 67% in HPA, carbapenem resistance in 13% in OPD vs. 40% in LPA vs. 47% in HPA. Among the *K. pneumoniae* isolates 3rd generation cephalosporin resistance was identified in 78% in OPD vs. 91% in LPA vs. 100% in HPA, fluoroquinolone resistance was in 64% in OPD vs. 86% in LPA vs. 80% in HPA, piperacillin resistance in 53% in OPD vs. 75% in LPA vs. 56% in HPA, carbapenem resistance in 14% in OPD vs. 67% in LPA vs. 55% in HPA. Among the *Enterococcus* isolates, vancomycin resistance was observed in 21% in OPD Vs. 24% in hospitalized cases. **Conclusion:** *E. coli* and *K. pneumoniae* together accounted for about two third microbiologically confirmed cases. Carbapenem resistance of about 10% in OPD cases and 50% in hospitalized patients seems alarming. Customized Anti microbial stewardship program (AMSP) at each health care facility is need of the hour.

Keywords: Urinary tract infections; Drug resistance; Microbial; Antimicrobial stewardship; Enterobacteriaceae; *Candida*; Gram positive bacteria

Introduction

The innovation of medical science brought a sea change in the evolution of humans from a mere short life-span nomad to a skilled long living being. One important tool in mankind's arsenal in this journey has been the discovery and invention of antimicrobials. Antimicrobials caused a drastic increase in life expectancy and more number of individuals entered elderly [1,2]. Evolution works for microbes as well. Indiscriminate usage of antimicrobials, culminated in artificial selection pressure amongst microbes making them more and more difficult to manage bugs in life threatening illness [3-8]. Anti microbial resistance (AMR) is now a global health crisis, with the World Health Organization (WHO) calling it "one of the biggest threats to global health, food security, and development today" and declared it as one of the top 10 threats to global health [9]. The overuse and misuse of antibiotics is one of the driving forces for development of AMR. Urinary tract infection (UTI) is one of the most common

infection for which antibiotics are prescribed. With an estimate of 150 million cases per year globally UTI is the 2nd most common infection among hospitalized patients globally with a cumulative healthcare cost expenditure of about \$6 billion annually [10-13].

Although the microbiological causative agent in UTI varies as per age, gender and comorbidity, *Escherichia coli* is the single most causative organism globally and across all age ranges. The other common organisms are *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Streptococcus agalactiae*, *Candida* etc. Community acquired urinary tract infections (Com. UTI) outnumber significantly to Health care associated UTI (HAI UTI) [13]. In view of extremely common occurrence of Com. UTI and minimal / absence of microbiological laboratory with culture & sensitivity facility, UTI are most of the times treated empirically. However, in absence of the local microbiological epidemiology and their antibiogram, most of the health care facilities depend on western guidelines for empirical management [14-16].

The present study was conceived at a central government tertiary level health care institute of central India to identify the microbiological epidemiology and their susceptible antibiogram

for consolidating Indian evidence.

Methods

Study Design and Setting: This study was designed as a prospective cross sectional study at AIIMS, Bhopal an institute of national importance from January 2020 to December 2021 as part of Indian Council of Medical Research (ICMR) Anti Microbial Resistance and Surveillance Network (AMRSN).

Study Participants:

Inclusion criteria:

1. Patients presenting with at least one symptoms of UTI (fever, dysuria, urinary urgency, increased urinary frequency, supra pubic discomfort, flank pain, fever, haematuria or pyuria) or any other symptom with physician presumptive diagnosis *and*
2. Patients attending Outpatient department (OPD) or hospitalised to low priority area (LPA) like general ward or to high priority area (HPA) like Intensive Care Unit (ICU) or High Dependency Unit (HDU) *and*
3. Urine was sent for microbiological culture and sensitivity testing

Exclusion criteria: None

Study procedure

The study was conducted after approval of institutional ethics committee (IHEC-LOP/2018/EF0080) and funded by Indian Council of Medical Research (ICMR).

Urine samples from patients were collected by a standard midstream clean catch method or by aseptically inserting a needle into the Folly's catheter. The collected specimens were promptly transported to the laboratory as soon as possible and were processed on Cystine lactose electrolyte deficient (CLED) agar, preferably within 2 hours. Cultures were incubated in aerobic atmosphere at 37°C for 48 hrs and observed daily. A positive urine culture was defined as colony count $\geq 10^5$ CFU/ml for midstream urine or catheterized patients in a symptomatic patient. Contamination was considered when more than two different types of growth are present. Asymptomatic patients were excluded. All positive cultures were further identified by their colony characteristics. Final confirmation was done by conventional biochemical methods or using automated systems Vitek2® (BioMérieux, Marcy, l'Étoile, France). Antimicrobial susceptibility test was carried out using the Kirby-Bauer disc diffusion method as per the Clinical Laboratory Standards Institute (CLSI) guidelines on Muller Hinton agar [17]. Samples growing more than two organisms were discarded as contaminant. We diagnosed HAI UTI if the symptoms of UTI developed after 2 calendar days of catheterization or any other urological instrumentation. The schematic flow chart of study procedure is provided in Figure 1.

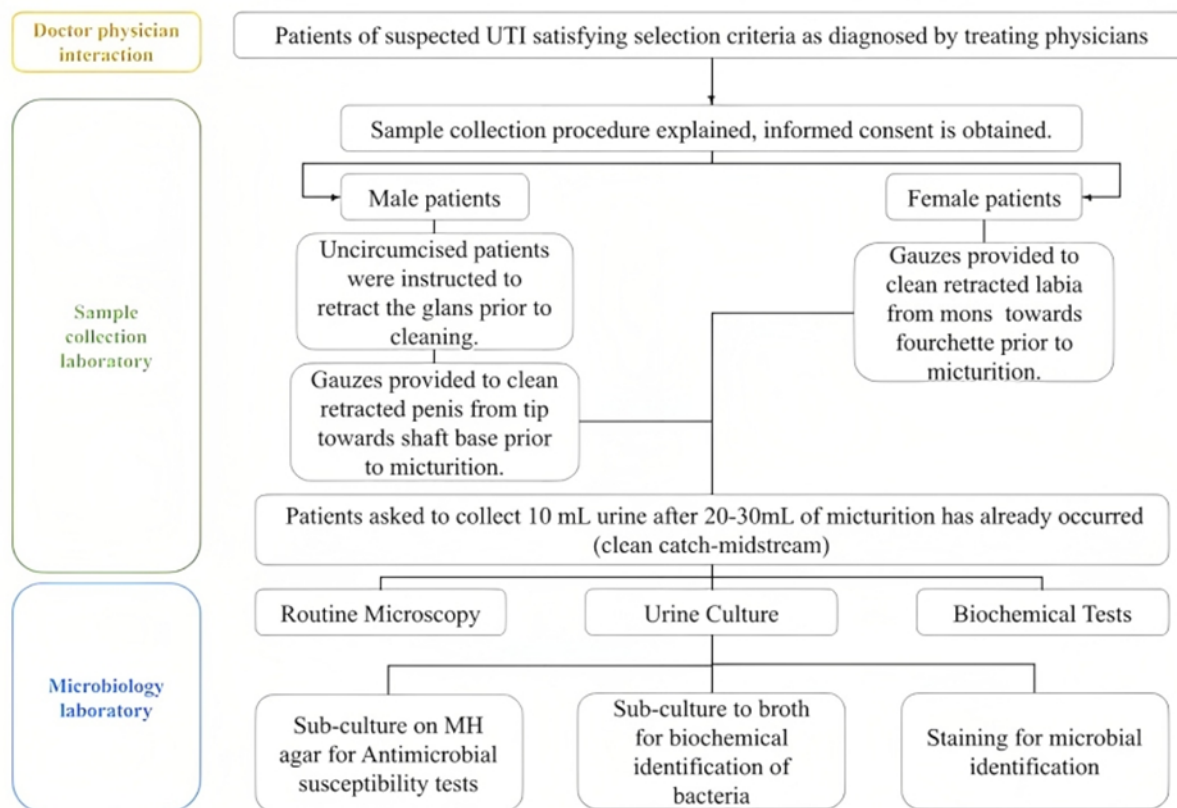


Figure 1: Schematic flowchart of urine sample collection and analysis.

Result

A total of 14526 patients were symptomatic and suspected for UTI. Out of these patients, 58.0% (8428/14526) were from out-patients department, 35.9% (5226/14526) were hospitalized in low priority area (LPA) like general wards and 6.0% (872/14526) were hospitalized in high priority area (HPA) like Intensive Care Unit (ICU) or High Dependency Unit (HDU). Out of the 6098 (5226+872) hospitalized patients, 85.7% (5226/6098) were from LPA and 14.2% (872/6098) were from HPA.

Among the 14526 patients of symptomatic UTI cases, microbiological culture positive rate was 15.2% (2222/14526). Among the 2222 number of microbiological culture positive cases of UTI, 67.9% (1510/2222) were community acquired UTI (Com. UTI), 8.3% (186/2222) were hospital acquired catheter associated UTI (CAUTI) and 23.6% (526/2222) of cases could not be differentiated into either Com. UTI or CAUTI. Among the 1510 number of Com. UTI cases, 55.9% (845/1510) cases presented in outpatient department (OPD), 39.8% (602/1510) were hospitalized in LPA and 4.1% (63/1510) were hospitalized in HPA.

Among the 1510 microbiologically proven culture positive Com. UTI cases, Gram negative bacilli (GNB) were isolated in 88.7% (1340/1510), Gram positive cocci (GPC) were isolated in 10.1% (154/1510) and candida in 1.0% (16/1510) cases. The top three GNB uro-pathogens isolated were *Escherichia coli* 58.9% (890/1510), followed by *Klebsiella pneumoniae* 15.4% (233/1510) and *Pseudomonas aeruginosa* 4.2% (64/1510). Among the GPC, *Enterococcus* was isolated in 8.5% (129/1510) of cases followed by *Staphylococci* in 1.6% (25/1510) cases. The detailed frequency and distribution of various uro-pathogens isolated from different areas are provided in Table 1.

Uro-pathogen	No. of isolates			
	Total	OPD	LPA	HPA
Gram Negative Bacilli (GNB), n=1340				
<i>Escherichia coli</i>	890	585	286	19
<i>Klebsiella pneumoniae</i>	233	111	111	11
<i>Pseudomonas aeruginosa</i>	64	24	35	5
<i>Acinetobacter baumannii</i>	27	11	14	2
<i>Klebsiella oxytoca</i>	20	7	12	1
<i>Enterobacter</i> spp.	18	10	8	0
<i>Proteus mirabilis</i>	17	9	8	0
<i>Morganella morganii</i>	16	7	9	0
<i>Acinetobacter</i> spp.	11	3	8	0
<i>Citrobacter koseri</i>	9	4	5	0
<i>Klebsiella</i> spp .	8	3	5	0
<i>Enterobacter cloacae</i>	8	3	5	0
<i>Acinetobacter baumannii-calcoaceticus complex</i>	6	0	4	2
<i>Proteus vulgaris</i>	5	3	2	0
<i>Acinetobacter baumannii-calcoaceticus complex</i>	3	3	0	0
<i>Citrobacter</i> spp.	2	0	2	0
<i>Citrobacter freundii</i>	1	1	0	0
<i>Providencia rettgeri</i>	1	0	0	1
<i>Acinetobacter lwoffii</i>	1	1	0	0
Gram Positive Cocci (GPC), n=154				
<i>Enterococcus</i> spp.	50	22	27	1
<i>Enterococcus faecium</i>	47	6	34	7
<i>Enterococcus faecalis</i>	32	15	15	2
<i>Staphylococcus aureus</i>	17	11	5	1
<i>Staphylococcus epidermidis</i>	5	4	1	0
<i>Staphylococcus haemolyticus</i>	1	0	1	0
<i>Staphylococcus</i> spp.	1	0	1	0
<i>Staphylococcus saprophyticus</i>	1	1	0	0
Fungus, n=16				
<i>Candida tropicalis</i>	8	0	1	7
<i>Candida auris</i>	5	1	3	1
<i>Candida albicans</i>	2	0	0	2
<i>Candida glabrata</i>	1	0	0	1
Grand Total	1510	845	602	63

OPD= outpatient department, LPA= low priority area, HPA= high priority area.

Table 1: The frequency and distribution of various Uro-pathogens isolated during the study period.

Of the *E. coli* isolates, 65.7% (585/890) cases were from OPD, 32.1% (286/890) of cases were hospitalized in LPA, and 2.1% (19/890) in HPA. *E. coli* isolated from OPD cases showed 84% resistance to 3rd generation cephalosporin, 82% resistance to fluoroquinolones, 38% resistance to piperacillin and 13% resistance to carbapenem. The *E. coli* isolates from the LPA, showed 92% resistance to 3rd GCR, 94% resistance to fluoroquinolones, 63% resistance to piperacillin and 40% resistance to carbapenems. The *E. coli* isolates from HPA, showed 100% resistance to 3rd GCR, 100% resistance to fluoroquinolones, 67% resistance to piperacillin and 47% resistance to carbapenem. The percentage susceptibility antibiogram of *E. coli* in different areas of hospital is summarized in Table 2.

Of the *Klebsiella pneumoniae* isolates, 47.6% (111/233) cases were isolated from OPD, 47.6% (111/233) were hospitalized in LPA and 4.7% (11/233) in HPA. *Klebsiella pneumoniae* isolated from OPD cases showed 78% resistance to 3rd generation cephalosporin, 64% resistance to fluoroquinolones, 53% resistance to piperacillin and 14% resistance to carbapenem. The *Klebsiella pneumoniae* isolates from the LPA, showed 91% resistance to

3rd generation cephalosporin, 86% resistance to fluoroquinolone, 75% resistance to piperacillin and 67% resistance to carbapenem. The *Klebsiella pneumoniae* isolates from the HPA, showed 100% resistance to 3rd generation cephalosporin, 80% resistance to fluoroquinolone, 56% resistance to piperacillin and 55% resistant to carbapenem. The percentage susceptibility antibiogram of *Klebsiella pneumoniae* in different areas of hospital is summarized in Table 2.

Of the *Pseudomonas aeruginosa* isolates, 37.5% (24/64) cases were isolated from OPD patients, 54.6% (35/64) were hospitalized in LPA and 7.8% (5/64) in HPA. *Pseudomonas aeruginosa* isolated from OPD cases showed 38% resistance to 3rd generation cephalosporin, 25% resistance to fluoroquinolone, 31% resistance to piperacillin and 37% resistance to carbapenem. The *Pseudomonas aeruginosa* isolates from the LPA, showed 52% resistance to 3rd generation cephalosporin, 66% resistance to fluoroquinolone, 58% resistance to piperacillin and 54% resistance to carbapenem. The percentage susceptibility antibiogram of *Pseudomonas aeruginosa* isolates in different areas of hospital is summarized in Table 2.

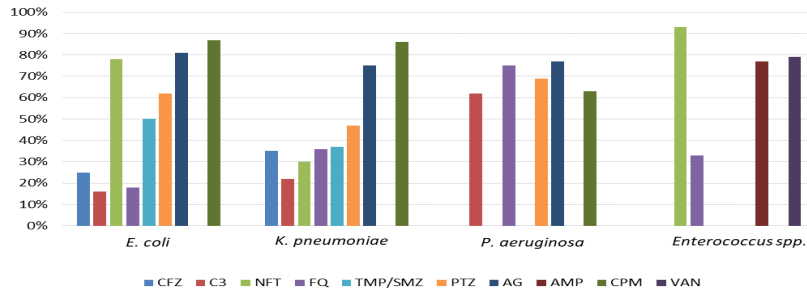
Area	Uro-pathogens	CFZ	C3	NFT	FQ	TMP/SMZ	PTZ	AG	AMP	CPM	VAN
OPD	<i>Escherichia coli</i> (n=585)	25%	16%	78%	18%	50%	62%	81%	ND	87%	ND
	<i>Klebsiella pneumoniae</i> (n=111)	35%	22%	30%	36%	37%	47%	75%	ND	86%	ND
	<i>Pseudomonas aeruginosa</i> (n= 24)	ND	62%	ND	75%	ND	69%	77%	ND	63%	ND
	<i>Enterococcus</i> (n=43)	ND	ND	93%	33%	ND	ND	77%*	77%	ND	79%
LPA	<i>Escherichia coli</i> (n=286)	9%	8%	67%	6%	26%	37%	59%	ND	60%	ND
	<i>Klebsiella pneumoniae</i> (n=111)	15%	9%	18%	14%	32%	25%	31%	ND	33%	ND
	<i>Pseudomonas aeruginosa</i> (n= 35)	ND	48%	ND	34%	ND	42%	52%	ND	46%	ND
	<i>Enterococcus</i> (n=76)	ND	ND	42%	4%	ND	ND	39%*	31%	ND	76%
HPA	<i>Escherichia coli</i> (n=19)	0%	0%	72%	0%	18%	33%	54%	ND	53%	ND
	<i>Klebsiella pneumoniae</i> (n=11)	29%	0%	9%	20%	40%	44%	50%	ND	45%	ND

OPD=outpatient department; LPA=low priority area; HPA=high priority area; CFZ=cefazolin; NFT=nitrofurantoin; FQ=fluoroquinolone; TMP/SMZ=trimethoprim-sulfamethoxazole; C3=3rd-generation cephalosporins; PTZ=piperacillin-tazobactam; AG=aminoglycosides; AMP=ampicillin; CPM=carbapenems; VAN=vancomycin; ND=not done, *= high dose aminoglycoside

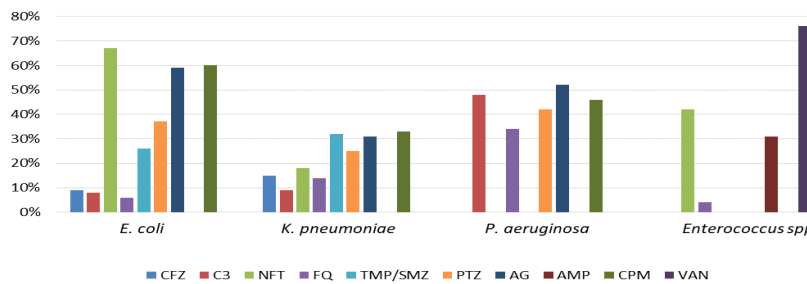
Table 2: Antibiogram (% Susceptibility profile) of uro-pathogens isolated from different areas of hospital.

Among the *Enterococcus* isolates, vancomycin resistance was observed in 21% in OPD Vs. 24% in hospitalized cases. The comparative analysis of various dominant uro-pathogens in different areas of hospital (OPD, LPA and HPA) is represented in Figure 2.

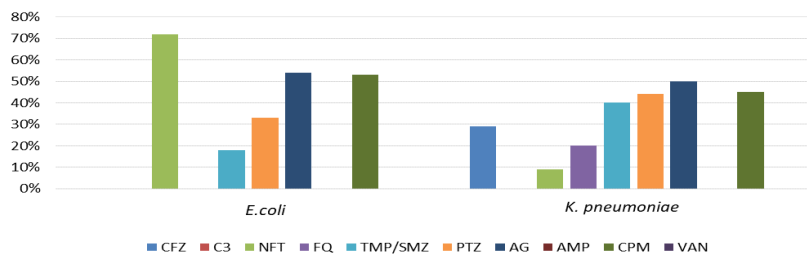
A-OPD



B- LPA



C- HPA



A: Antibiogram (% Susceptibility profile) of uro-pathogens isolated from outpatient department (OPD) of hospital
 B: Antibiogram (% Susceptibility profile) of uro-pathogens isolated from low priority area (LPA) of hospital
 C: Antibiogram (% Susceptibility profile) of uro-pathogens isolated from high priority area (HPA) of hospital

Figure 2: Comparative susceptibility antibiogram of dominant uro-pathogens in different areas.

Discussion

UTIs are one of the most common infections globally for which antibiotics are used and possess a major challenge in management. There is a difference in spectrum of organisms causing UTI, their prevalence and antimicrobial susceptibility in different regions. Our study describes the antimicrobial susceptibility pattern of dominant uro-pathogens in community acquired UTI cases.

The overall microbiological culture positive rate was 15.2% among the symptomatic UTI cases in our study. The culture positivity rate varies from 8.6% to 57.8% in various studies [18]. In the present study, *E. coli* (58.9%) followed by *Klebsiella pneumoniae* (15.4%) was the most common pathogen. This is in accordance to earlier studies from different regions of India and other countries [11,15,19]. In our study these two organisms were responsible for 74.3% of cases.

There is a global surge in UTI cases caused by extended-spectrum β -lactamase (ESBL) producing organisms across the globe. ESBL-producing pathogens often manifest resistance determinants to several antibiotic groups like aminoglycosides

and fluoroquinolones, which limit the range of effective antibiotics [18]. In our study, *Escherichia coli* and *K. pneumoniae*, showed extremely high resistance to 3rd generation cephalosporin, fluoroquinolone, piperacillin and carbapenem among patients from OPD or LPA / HPA as described in Table-2. Another study from India, also documented similar higher resistance to fluoroquinolone, piperacillin and carbapenem [20]. Stapleton et al. (2017), reported that multi drug resistant *E. coli* associated hospital and community-acquired UTI have increased over 10 years, except for nitrofurantoin and gentamicin [21].

In our study, carbapenem resistance was identified in 13%, 40% and 47% among *E. coli* isolates in OPD, LPA and HPA respectively. Among isolates of *K. pneumoniae*, carbapenem resistance was 14%, 67% and 57% respectively in OPD, LPA and HPA. Our study is comparable to the earlier study from India by Walia et al. (2022) where carbapenem resistance was as high as 62% for *E. coli* and 76.3% in *K. pneumoniae*. However, the menace of carbapenem resistant organisms seems to be much less in other part of the world [15,22,26-28]. The prevalence of carbapenem resistance among *Escherichia coli* and *K. pneumoniae* in various countries is summarized in Table 3.

Study group	Country	<i>E. coli</i> (% Resistance)	<i>K. pneumoniae</i> (% Resistance)
Current study	India	13 (OPD) 40 (LPA) 47% (HPA)	14.0 (OPD) 67 (LPA) 55 (HPA)
Walia et al. [22]	India	62.0	76.3
Erastus et al. [26]	Namibia	1.0	NA
Ian et al. [27]	European	0.6	12.0
Zilberberg et al. [28]	USA	15.2	37.4
Islam et al. [15]	Bangladesh	5.0	9.0

OPD: Outpatient department, LPA: low priority area, HPA: high priority area.

Table 3: Comparative analysis of carbapenem resistance among *E. coli* and *K. pneumoniae*.

Among the *Enterococcus* isolates, vancomycin resistance was observed in 21% in OPD cases and 24% in hospitalized cases. Similar higher prevalence vancomycin resistant *Enterococcus* isolates have also been documented (11%-20%) in other parts of India [22,23].

Apart from gram negative and gram positive bacteria, various species of *Candida* were isolated from 1.0% (16/1510) of the microbiologically proven culture positive urine samples. The prevalence of UTI associated with *Candida spp.* was similar to a study from Italy by Serretiello et.al. (2021), but lower than another study from western India conducted by Patel et. al (2019) which documented 18.5% [11,14].

Strength and Limitations

Our study has several strengths. To the best of our knowledge, this is the first ever study from central India studying the susceptibility pattern of uro-pathogens from both OPD and hospitalized patients in a real life scenario. Even with best of efforts, a significant amount of patients could be categorized into

Com. UTI or HAI UTI. The outcome for discharge / death was not studied.

Conclusion

The present study identifies the increasing incidence of multi drug resistance among the dominant pathogens causing UTI especially in *E. coli* and *K. pneumoniae*. The prevalence of carbapenem resistance more than 10% among out patients and about 50% among the hospitalized patients seems alarming. Antimicrobial stewardship program (AMSP) in low and middle-income countries is challenging yet an urgent need especially true for most Asian countries [24,25]. A customized robust AMSP at each of the health care facilities is the need of the hour.

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Conflict of Interest: The Authors declare no conflicts of interest among authors.

Author Contribution:

Author	Concept	Design	Data acquisition	Data Analysis	Manuscript preparation	Manuscript editing	Manuscript review
TK	✓	✓	✓	✓	✓	✓	✓
ShK	-	-	-	✓	✓	✓	✓
RG	-	-	-	✓	✓	✓	✓
SS	-	-	✓	✓	✓	✓	✓
LP	-	-	-	✓	✓	✓	✓
KP	-	-	-	✓	✓	✓	✓
AnS	-	-	-	✓	✓	✓	✓
Eh	-	-	-	-	✓	✓	✓
AV	-	-	-	-	✓	✓	✓
RY	-	-	✓	-	✓	✓	✓
DB	-	-	-	-	✓	✓	✓
NJ	-	-	-	-	✓	✓	✓
ASR	-	-	-	-	✓	✓	✓
NU	-	-	-	-	✓	✓	✓
RaB	-	-	✓	✓	✓	✓	✓
SS	-	-	✓	✓	✓	✓	✓
AJ	-	-	-	-	✓	✓	✓

MP	-	-	-	-	✓	✓	✓
NK	-	-	-	-	✓	✓	✓
SP	-	-	-	-	✓	✓	✓
SK	✓	✓	✓	✓	✓	✓	✓

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