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Research Article

Antimicrobial Resistance Trends in Urinary Tract Infection at Secondary Care Centres in Central India: Carbepenem Resistance Crossing 20% in Community

Apurva Vyas[1], T Karuna[2], Shweta Kumar[3], Ayush Gupta[4], Ananyan Sampath[5], Pramod Goel[6], Pankaj Shukla[7], Vivek Mishra[8], Sandeep Sharma[9], Sourabh Chakraborty[10], Shree Prakash Jaiswal[11], Abhi Mishra[12], Apoorwa Gupta[13], Manisa Sahu[14], Shreshtha Tiwari[15], Anisa Pal[16], Manish Nagendra[17], Harish Gautam[18], Kamlesh Patel[19], Shruti Asati[20], Mukul Nema[21], Sagar Khadanga[22]

[1]Scientist C, Department of General Medicine, AIIMS Bhopal, Madhya Pradesh, India

[2]Additional Professor, Department of Microbiology, AIIMS Bhopal, Madhya Pradesh, India

[3]Research Associate III, Department of General Medicine, AIIMS Bhopal, Madhya Pradesh, India

[4]Assistant Professor, Department of Microbiology, AIIMS Bhopal, Madhya Pradesh, India

[5]MBBS Student, AIIMS Bhopal, Madhya Pradesh, India

[6]Deputy Director, Quality Assurance, Govt. of Madhya Pradesh, India

[7]Ex. Director, National Health Mission, Govt. of Madhya Pradesh, India

[8]State Consultant, Quality Assurance, Govt. of Madhya Pradesh, India

[9]State Consultant, Quality Assurance, Govt. of Madhya Pradesh, India

[10]Consultant- Microbiology, Bansal Hospital, Bhopal, Madhya Pradesh, India

[11]Head of the Department, Pathology Department, Choithram Hospital, Indore, Madhya Pradesh, India

[12]Microbiologist, Govt. P C Sethi Hospital, Indore, Madhya Pradesh, India

[13]Microbiologist, Rajshree Apollo Hospital, Indore, Madhya Pradesh, India

[14]Senior Consultant- Microbiology, Balco Medical centre, Raipur, Chhattisgarh, India

[15]Consultant-MicrobiologyICO, Balco Medical centre, Raipur, Chhattisgarh, India

[16]Microbiologist, Jabalpur Hospital and Research Centre, Jabalpur, Madhya Pradesh, India

[17]Associate Professor, Netaji Subhash Chandra Bose Medical college, Jabalpur, Madhya Pradesh, India

[18]Microbiologist, Govt. Jai Prakash Hospital, Bhopal, Madhya Pradesh, India

[19]Microbiologist, Medanta Hospital, Indore, Madhya Pradesh, India

[20]Assistant Professor, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

[21]CEO and Quality Head, Anant Nursing Home PVT. LTD. Jabalpur, Madhya Pradesh, India

[22]Associate Professor, Department of General Medicine, AIIMS Bhopal, Madhya Pradesh, India

*Corresponding author: Sagar Khadanga, Associate Professor, Department of General Medicine, AIIMS Bhopal, Madhya Pradesh, India

Abstract

Background: Urinary tract Infection (UTI) is a significant global health burden, with high morbidity and mortality especially in developing nations. This study assessed the changing pattern of anti-microbial resistance (AMR) in UTI in secondary care centres of central India. **Methodology:** This was a prospective observational study conducted in 10 secondary care centres in smaller cities of Central India in the state of Madhya Pradesh. **Result:** Among the 8856 number of symptomatic urinary tract infections whose urine was sent for microbiological culture and sensitivity, 2409 (27.2%) showed significant pathological growth out of which 92.1% (2221/2409) showed bacterial growth and 7.8% (188/2409) showed fungal growth. Gram-negative bacteria accounted for 85.0% (1890/2221) and Gram-positive bacteria for 14.9% (331/2221). *E. coli* was the most prevalent Gram-negative isolate (57.4%), followed by *K. pneumoniae (21.3%), Pseudomonas aeruginosa* (12.1%). Third generation cephalosporin resistance was observed in 76.2% in *E. coli* and 71.6% in *K. pneumonia*. Carbapenem resistance was highest in *P. aeruginosa* (61.8%) followed by *Acinetobacter spp* (52.2%), *Enterobacter spp.* (50%), *K. pneumoniae* (35.4%) and *E. coli* (22.6%). Colistin resistance was observed in *Enterobacter spp.* (15.0%) followed by *Acinetobacter spp* (9.1%), *K. pneumoniae* (7.6%), *E. Coli* (6.9%) and *P. aeruginosa* (4.9%). Among the gram-positive isolates, 47.5% of *Staphylococcus aureus* were Methicillin resistant and 3.7% were resistance to vancomycin. Among the *Enterococcus spp.* 14.1% were resistance to vancomycin. **Conclusion:** It is of great concern, that 20% of *Escherichia coli* and *Klebsiella pneumonia* islates are resistant to carbpenems in community settings at smaller cities in India. Though negligible, UTI caused by VRSA and VRE cannot be neglected. There is definitely a rise the occurrence of UTI caused by *Candida*.

Introduction

A Urinary Tract Infections (UTI) is an infection in any part of the urinary system. The urinary system includes the kidney, ureter, bladder and urethra. Depending on the site of the infection, UTI is classified as urethritis (infection of the urethra), cystitis (inflammation of the bladder) and pyelonephritis (infection of the kidney). UTI are among the most common infectious diseases affect approximately 150 million people worldwide every year [1-3]. UTI can be healthcare-associated or community-acquired based on how the infections are acquired. Usually, community-acquired UTIs are more prevalent than hospital-acquired UTIs [4]. UTIs can also be clinically classified as complicated and uncomplicated. Community acquired UTIs are usually uncomplicated while hospital-acquired UTIs are complicated.

UTIs are caused by a wide range of pathogens, including Gram negative bacilli (GNB), Gram positive cocci (GPC), as well as fungi. UTIs can affect individuals of all sexes and age group, with the incidence rate increasing with age. UTIs are considerably more common in women than in men due to anatomic and physiological reasons. Approximately 50%-60% women get at least one UTI in their lifetime and 20-40% of women have a recurrent episodes [5,6]. UTIs cases among children is reported to be 30% all over the world [7].

UTIs are primarily caused by bacteria and often treated by broad spectrum antibiotics which leads to increased antibiotic usage and has resulted in development of antibiotic resistance in bacteria. In majority of cases, antibiotics treatment is prescribed empirically before the laboratory report of urine culture are available. Correct selection of antibiotic treatment is thus crucial, as inappropriate use could contribute to the alarming increase in antimicrobial resistance (AMR) [8]. Continuous surveillance and monitoring of local antimicrobial resistance pattern should be conducted regularly to help the clinicians with a better antibiotic therapy decision. However, most of the centres in Indian subcontinent lack local antibiogram adding the vicious cycle of ill managed antibiotic usage and AMR.

Indian Council of Medical Research (ICMR) has initiated nationwide "Antimicrobial Resistance Surveillance and Research Network" (AMRSN) [9]. Madhya Pradesh is a state in central India, having its own State Action Plan for containment of antimicrobial resistance (MPSAPCAR) which was developed in 2019 on the guidelines of National Action Plan on AMR. The present study was conducted with support from ICMR-AMRSN and MPSAPCAR. The study was conceived to identify the pattern of antibiogram for UTI in secondary care hospitals (district hospitals / nursing homes) at central India. The aim of the present study was to identify UTI related microbiological epidemiology and susceptible antibiogram of dominant uro-pathogens in of smaller cities in India. This study will consolidate Indian evidence with special reference to secondary care centres in community.

Methodology

AIIMS Bhopal is an institute of national importance (INI) in central India and part of ICMR-initiated AMRSN. The ICMR-AMSRN AIIMS Bhopal sub-network runs a regional anti-microbial stewardship program (AMSP) consisting of 10 centres (two government district hospitals and eight nursing homes) in smaller cities of Madhya Pradesh state in India. The location of these cities is presented in Figure 1. The cites were carefully nominated by the Government of Madhya Pradesh and ICMR-AMRSN, on the parameters of the availability of an in-house microbiology laboratory and a full-time microbiologist.
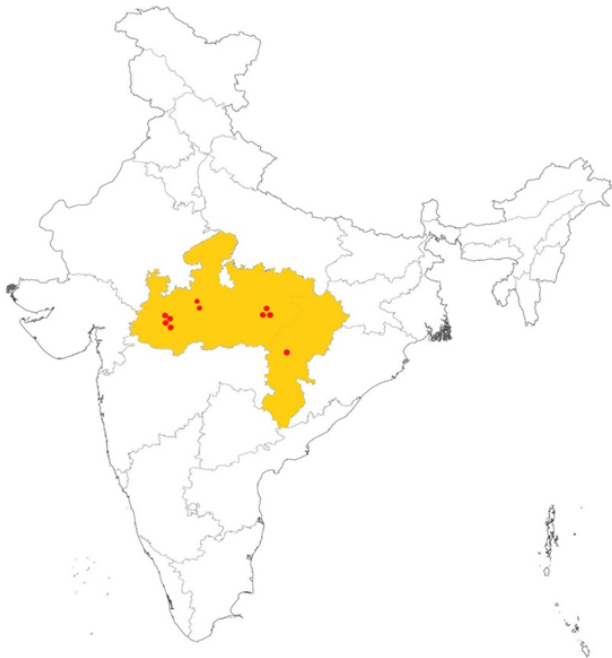

Figure 1: AIIMS Bhopal ICMR-AMRSN initiated network.

This figure is indicative of all centres selected for our study. Four centres from Indore (Madhya Pradesh), three from Jabalpur (Madhya Pradesh), two from Bhopal (Madhya Pradesh) and one from Raipur (Chhattisgarh).

The study was carried out as part of ICMR-AMRSN, with Institute Human Ethics Committee (IHEC) approval vide Letter No. LOP/2020/EF0157 dated February 24, 2020. As the study was only observational and with data obtained from chart reviews without any patient identifiers, a waiver of consent was granted by IHEC. The study procedure was in accordance with the principles of the Declaration of Helsinki.

Study setting: Among all the 52 districts of MP, only two district hospitals (DHs) possessed microbiological culture facilities and hence were included in the study. The remaining eight study sites were located in urban / semi-urban areas and were private nursing homes.

Study design: The current study was a prospective longitudinal observational chart review type of study. The present data set was collected from 1st April 2022 to 30 September 2022. Formal sample size was not calculated and planned for consecutive and feasible sampling during the study period.

Study procedure: All the 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) and hospitalised and urine was sent for microbiological culture and sensitivity testing were taken into the study.

Midstream urine and aspirated urine sample from the Foley's catheter sample were collected from non-catheterized and catheterized patients, respectively. 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. The plates were incubated at 35 ± 2^0 C under aerobic conditions for overnight incubation. Plates were examined each day for up to 48 hours for colonies of interest. Colonies growing in significant numbers were further identified by conventional biochemical tests and susceptibility testing by Kirby-Bauer disk-diffusion method. Results of antimicrobial susceptibility were interpreted as per CLSI-M100. Samples with more than two growths were discarded as contaminant and asked to repeat the test.

Antibiogram was generated only for those organisms with a cumulative frequency of more than 30 samples. Speciation of *Acinetobacter* spp. and *Enterococcus* spp. isolates could not be done due to the unavailability of resources at these smaller secondary centres. Third-generation cephalosporin resistance for the *Enterobacteriaceae* family was tested using ceftriaxone and

for *Pseudomonas* using ceftazidime and was calculated by 100 minus the susceptibility percentage of ceftriaxone/ceftazidime. Carbapenem resistance was calculated by 100 minus the susceptibility percentage of meropenem. Methicillin resistance was calculated by 100 minus the susceptibility percentage of oxacillin. Cleaned data were entered in a Microsoft Excel spreadsheet. The data were summarized as frequencies and percentages up to one decimal value.

Result

Out of the 8856 urine samples, 2409 (27.2%) showed significant pathological growth. Among the positive cultures (n=2409), 2221 (92.1%) showed bacterial growth, and 188 (7.8%) were *Candida spp*. Among the bacterial growth (n=2221), 1890 (85.0%) were Gram negative bacilli (GNB), and 331 (14.9%) were Gram positive cocci (GPC). Among the GNB isolates (n=1890), the predominant isolate was *Escherichia coli* (1086, 57.4%) followed by *Klebsiella pneumoniae* (403, 21.3%) and *Pseudomonas aeruginosa* (229, 12.1%). The prevalence of other isolates is given in details in Table-1. The susceptibility patterns of the identified pathogens to different antibiotics were analysed and provided below.

Total culture positive isolates	27.2% (2409/8856)
Total bacterial isolates	92.1% (2221/2409)
Gram-Negative Bacilli (GNB)	**78.4% (1890/2409)**
Escherichia coli	45.0% (1086/2409)
Klebsiella pneumoniae	16.7% (403/2409)
Pseudomonas aeruginosa	9.5% (229/2409)
Enterobacter spp.	6.1% (148/2409)
Acinetobacter spp.	0.9% (23/2409)
Salmonella spp.	0.0% (1/2409)
Gram-Positive Cocci (GPC)	**13.7% (331/2409)**
Enterococcus spp.	11.4% (277/2409)
Staphylococcus aureus	2.2% (54/2409)
Candida spp.	**7.8% (188/2409)**

Table 1: Spectrum of culture positive isolates.

Escherichia coli: Resistance to 3rd generation cephalosporin was noticed in 76.2% cases. Piperacillin in 37.3% cases, carbapenem resistance in 22.6% and colistin resistance in 6.9% cases. The detailed anibiogram of *Escherichia coli* is provided in Figure-2(A).

Klebsiella pneumoniae: Resistance to 3rd generation cephalosporin was noticed in 71.6% cases. Piperacillin in 46.4% cases, carbapenem resistance in 35.4% and colistin resistance in 7.6% cases. The detailed anibiogram of *Klebsiella pneumoniae* is provided in Figure-2(B).

Enterobacter spp.: Resistance to 3rd generation cephalosporin was noticed in 74.7% cases. Piperacillin in 54.3% cases, carbapenem resistance in 50% and colistin resistance in 15% cases. The detailed anibiogram of *Klebsiella pneumoniae* is provided in Figure-2(B).

Pseudomonas aeruginosa: Resistance to 3rd generation cephalosporin was noticed in 73.4% cases. Piperacillin in 68.9% cases, carbapenem resistance in 61.8% and colistin resistance in 4.9% cases. The detailed anibiogram of *Pseudomonas aeruginosa* is provided in Figure-2(C).

Acinetobacter spp.: Resistance to Piperacillin was noticed in 54.5% cases. Carbapenem resistance in 52.2% and colistin resistance in 9.1% cases. The detailed anibiogram of *Acinetobacter spp* is provided in Figure-2(D).

Enterococcus spp.: Vancomycin resistance was seen in 14.1% of cases and linezolid resistance in 4.3% of cases. The detailed antibiogram of *Enterococcus* isolates is provided in Figure-2(E).

Staphylococcus aureus: Vancomycin resistance was seen in 3.7% of cases and linezolid resistance in 9.3% of cases. The detailed antibiogram of *Staphylococcus aureus* isolates is provided in Figure-2(F).
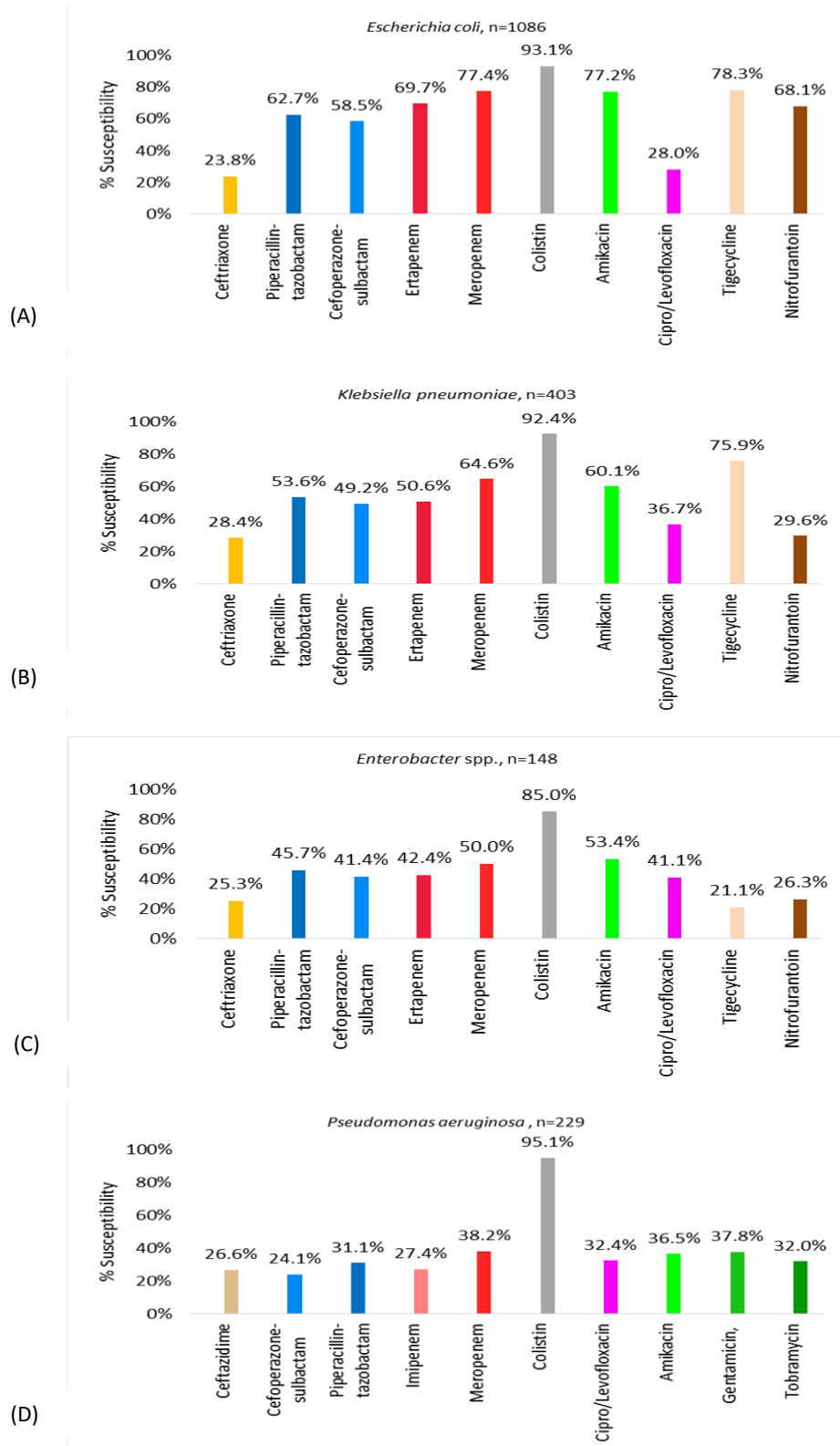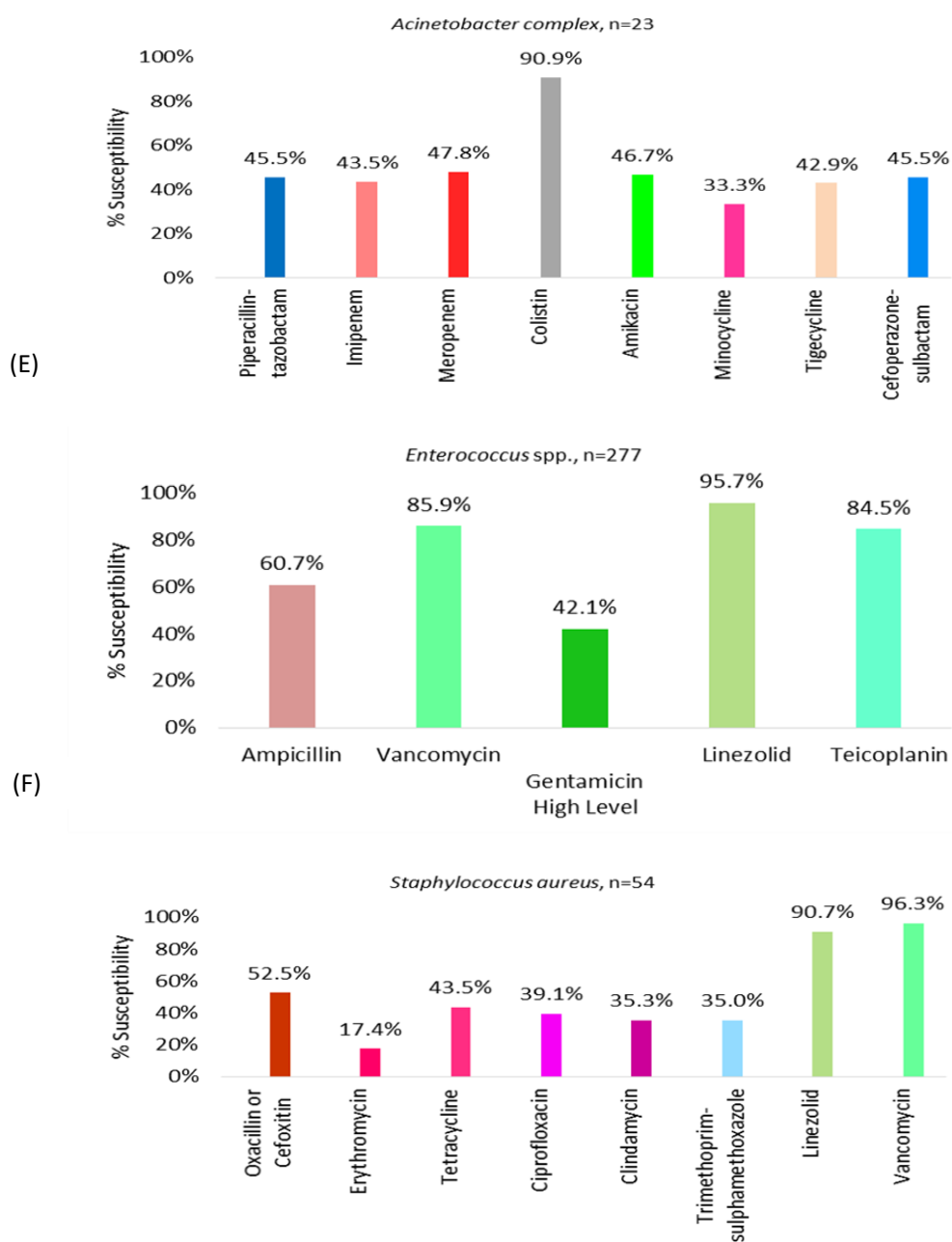
Figure 2: *Escherichia coli* (B) *Klebsiella pneumoniae* (C) *Enterobacter spp.* (D) *Pseudomonas aeruginosa* (E) *Acinetobacter spp.* (F) *Enterococcus spp.* (G) *Staphylococcus aureus*

Discussion

In our study, among the symptomatic UTI patients, the microbiological culture positivity rate was 27.2%. Other studies from India and abroad documented the culture positivity rate from as low as 13.6% in Shanghai to 79.9% in Uttar Pradesh, India [10-17]. This variation may be due to many factors like age and gender, associated co morbidity and geographical locations.

Like all other studies across the globe as mentioned above, in the present study, UTI due to GNB was more common. In the present study *Escherichia coli* was the most common organism followed by *Klebsiella pneumoniae*. Previous studies from different region of India and from other countries have reported the similar scenario [5,18-22]. However, Muktikesh et.al. who found out that *Escherichia coli* (68.8%) was the commonest organism followed by *Enterococcus spp.* (9.7%) [23].

In the present study *Escherichia coli* showed highest resistance against 3rd generation cephalosporine. The resistance of *Escherichia coli* to 3rd generation cephalosporine varies from 7.8% to 92.2% across the globe [1,8,16,20,21,24-37]. The comparative analysis of *Escherichia coli* resistance pattern from various studies across the globe, is provided in Table-2.

Organism	Category	Present Study	India [17]	Ethiopia [37]	Saudi Arabia [29]	Central Europe [26]	Bangladesh [36]	Turkey [21]
Escherichia coli	3rd GCR	76.2%	83.1%	58.4%	46.1%	9.5%	58.6%	92.2%
	Carba R	22.6%	62.8%	3.3%	0.0%	0.0%	1.4%	9.1%
	Coli R	6.9%	NA	NA	0.0%	0.8%	NA	0.0%
Klebsiella pneumoniae	3rd GCR	71.6%	59.1%	70.6%	59.0%	34.3%	49.3%	100.0%
	Carba R	35.4%	59.1%	15.4%	25.0%	0.0%	0.0%	0.0%
	Coli R	7.6%	NA	NA	0.0%	2.0%	NA	NA
Enterobacter spp.	3rd GCR	74.7%	64.7%	38.0%	NA	NA	NA	NA
	Carba R	50.0%	70.6%	40.0%	NA	NA	NA	100.0%
	Coli R	15.0%	NA	NA	NA	NA	NA	NA
Pseudomonas aeruginosa	3rd GCR	73.4%	76.2%	14.3%	50.0%	18.7%	60.0%	25.0%
	Carba R	61.8%	76.2%	0.0%	28.5%	31.8%	17.2%	100.0%
	Coli R	4.9%	NA	NA	0.0%	0.0%	NA	0.0%
Acinetobacter spp.	Carba R	52.2%	NA	71.4%	NA	NA	NA	100.0%
	Coli R	9.1%	NA	NA	NA	NA	NA	NA

Staphylococcus aureus	MRSA	47.5%	85.0%	100.0%	NA	NA	NA	50.0%
	VRSA	3.7%	0.0%	NA	NA	NA	0.0%	0.0%
Enterococcus spp.	AMP R	39.3%	33.3%	50.0%	46.4%	10.6%	0.0%	25.0%
	VRE	14.1%	27.8%	50.0%	0.0%	1.0%	0.0%	50.0%

Table 2: Comparative analysis of dominant uro-pathogens.

3rdGCR- 3rd generation cephalosporin resistant, Carba R- Carbapenem resistant, Coli R- Colistin resistant, MRSA- Methicillin resistant Staphylococcus aureus, VRSA- Vancomycin resistant Staphylococcus aureus, AMP R- Ampicillin resistant, VRE- Vancomycin resistant Enterococcus.

In the present study 35.4% of *Klebsiella pneumoniae* isolates were resistant to meropenem. Meropenem resistance among *Klebsiella pneumoniae* isolates from urine has been observed from 0% to 52.2% across the globe [1,5,8,14,16,21,26-29,35-37]. The comparative analysis of *Klebsiella pneumoniae* resistance pattern from various studies across the globe, is provided in Table-2.

In our study *Pseudomonas aeruginosa* were highly resistant (>60%) to all the tested antibiotics (excluding colistin). Colistin susceptibility among *Pseudomonas aeruginosa* isolates was 95.1%. Studis from Central Europe, Turkey and Saudi Arabia reported similar data of susceptibility pattern [21,26,29]. The comparative analysis of *Pseudomonas aeruginosa* resistance pattern from various studies across the globe, is provided in Table-2.

Among the total *Staphylococcus aureus* isolates methicillin resistant *Staphylococcus aureus* (MRSA) was 47.5%. Similar incidences of MRSA in UTI were reported in studies from Saudi Arabia (50.0%), Turkey (50.0%) and Brazil (43.7%) [21,24,29]. A study from Benin by Assouma et. al. (2023) recorded 100% prevalence of MRSA [38]. Vancomycin resistant *Staphylococcus aureus* (VRSA) in our study was 3.7%. Higher rate of VRSA was reported in studies from Jharkhand, india (43.8%) and Benin (42.3%) [34,38]. On the other hand absence of VRSA were found in some other studies [20,21,29,36]. The comparative analysis of *Staphylococcus aureus* resistance pattern from various studies across the globe, is provided in Table-2.

In the present study, *Enterococcus spp.* were most susceptible to linezolid (95.7%) followed by vancomycin (85.9%). Contrary to our finding, some of the studies from India and abroad reported absence of vancomycin resistance [14,29,36]. On the other hand,

an extremely high rate of vancomycin resistance to the tune of 50%, was observed in studies from Turkey and Ethiopia [21,37]. The comparative analysis of *Enterococcus spp.* resistance pattern from various studies across the globe, is provided in Table-2.

Apart from GNB and GPC, *Candida spp.* was isolated from 7.8% of the positive urine samples from symptomatic UTI cases. The prevalence of 7.8% *Candida spp.* was higher compared to a study conducted in Italy by Serretiello et.al. (2021), reported the prevalence of 0.9% and was lower to a study conducted by Patel et. al (2019) reported 18.5% prevalence of *Candida spp.* [11,14]. The increase in UTI caused by *Candida*, may be in rise, as India being the diabetic capital of the world.

Limitation

This study was with some limitations. The data was from smaller nursing homes and district hospitals with not so stringent quality adherence. UTI could not be sub-classified into community acquired and hospital acquired. Clinical information regarding patient's age, sex, co-morbidities were not available and hence stratified data analysis could not be performed.

Conclusion

It is of great concern, that 70% of *Escherichia coli* and *Klebsiella pneumonia* islates are resistant *to* 3rd generation cephalosporine and more than 20% resistant to carbpenems in community settings at smaller cities in India. Though negligible, UTI caused by VRSA and VRE cannot be neglected. There is definitely a rise the occurrence of UTI caused by *Candida.*

It is imperative to practice a robust anti microbial stewardship program even in smaller secondary care centres. All health care delivery systems in Indian sub continent should routine identify susceptible antibiogram of dominant uro pathogen which will greatly help the treating physicians to choose an antibiotic empirically and hence helping the cause of reducing AMR.

Acknowledgements

Institutional Review Board Statement: This project was granted clearance by the institutional ethics committee of AIIMS Bhopal vide LOP/2020/EF0157 dated February 24, 2020.

Informed Consent Statement: This study was designed and carried out as per the guidelines of Helsinki, Good clinical practice guidelines and followed the ICMR ethics handbook at all stages of planning, data acquisition, analysis and dissemination. All participants were recruited after informed written consent as per ICMR guidelines.

Author's contribution details:

	Concept	Design	Data acquisition	Data Analysis	Manuscript preparation	Manuscript editing	Manuscript review
AV	-	-	✓	✓	✓	✓	✓
TK	✓	✓	✓	✓	✓	✓	✓
SK	-	-	✓	✓	✓	✓	✓
AYG	-	✓	✓	✓	✓	✓	✓
AS	-	-	-	✓	✓	✓	✓
PG	-	-	✓	✓	✓	✓	✓
PS	-	-	✓	✓	✓	✓	✓
VM	-	-	✓	✓	✓	✓	✓
SS	-	-	✓	✓	✓	✓	✓
SC	-	-	✓	-	✓	✓	✓
SPJ	-	-	✓	-	✓	✓	✓
AM	-	-	✓	-	✓	✓	✓
AG	-	-	✓	-	✓	✓	✓
MS	-	-	✓	-	✓	✓	✓
ST	-	-	✓	-	✓	✓	✓
AP	-	-	✓	-	✓	✓	✓
MN	-	-	✓	-	✓	✓	✓
HG	-	-	✓	-	✓	✓	✓
KP	-	-	✓	-	✓	✓	✓
SA	-	-	✓	-	✓	✓	✓
MN	-	-	✓	-	-	✓	✓
SKH	✓	✓	✓	✓	✓	✓	✓

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