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ORIGINAL RESEARCH

Epidemiology and antibiotic resistance pattern of gram-negative bacteria induced urinary tract infections (UTIs) in Manipur, North-East India

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ABSTRACT

Background: Due to the increasing scenario of UTI and the prevalence of antimicrobial resistance uropathogens, the study focuses on the prevailing gram-negative bacteria (GNB)causing UTI and its associated co-factors. **Methodology:** It is a retrospective cross-sectional study for a period of 3 years from January 2021 to December 2023 from patients suspected of UTI. Urine samples were collected and processed microbiologically according to SOP. Antibiotic susceptibility testing was performed by CLSI guidelines. **Result:** *E. coli* (60.8%, *n*=4333) and *Klebsiella* sp. (23.6%, *n*=4333) are the predominant GNB causing UTI. Female patients (59.8%, *n*=4333) in comparison to male patients were more affected. The age group 51 to 70 years (35%, *n*=4333) were more affected. The highest sensitivity was observed from fosfomycin (87.9%, *n*=4333), followed by amikacin (81.3%, *n*=4333). *Klebsiella* sp. has a higher rate of resistance to antibiotics. Among the *E. coli* and *Klebsiella* sp., 24.5% (*n*=3662) are susceptible strains, whereas 63.1% (*n*=3662) and 12.2% (*n*=3662) of the strains are multidrug-resistant (MDR) and extensively drug-resistant (XDR), respectively. **Conclusion:** In this region, the prevalence of UTIs has increased alarmingly in the last two to three years. The aetiological agent may vary depending on age, gender, and season. The source of isolation (ICU, OPD, or ward) may have an impact on the antimicrobial susceptibility pattern of the aetiological agent within a region. Strains from the ICU have more resistance frequencies. To reduce the prevalence of MDR and XDR, the study recommends a mandatory antibiogram profile before starting UTI treatment.

Keyword: UTI, *E. coli*, uropathogens, MRD, XRD.

INTRODUCTION

With a lifetime prevalence of 50–60% in adult women, urinary tract infections (UTIs) are the most prevalent outpatient infections. UTI involve infection by pathogen invasion in any region of the urinary system. UTI prevalence rises with age, and it is roughly twice as common in women over 65 as it is in the general female population [1]. According to estimates, there were 236,790 fatalities and 404.61 million cases worldwide in 2019. Over the past three decades, the burden of UTIs has varied by country, area, age, sex, and sociodemographic position [2]. In hospitalized patients, UTIs are associated with an attributed mortality rate of 2.3% and an estimated annual cost of $340 to $450 million in the United States [3,4]. Repeated recurrences, pyelonephritis with sepsis, kidney damage in young infants, preterm birth, and problems from repeated use of antibiotics, such as *Clostridium difficile* colitis and high-level antibiotic resistance, are serious aftereffects of UTI[5]. Bacteria are frequently identified as the causal cause of UTIs. Uropathogenic*Escherichia coli* (UPEC) is the most frequent cause of both simple and complex UTIs. *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, group *B streptococcus* (GBS), *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, and *Candida* sp. are other aetiological agents that have been reported [5].

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Serious implications in health care systems and economic growth have resulted from the rising incidence of UTIs and the high prevalence of antibiotic-resistant uropathogens. Hence, continuous evaluation of UTI, and its antimicrobial susceptibility pattern of the region can help in combating the burden of UTI. The study focuses on the prevailing gram-negative bacteria (GNB) associated with UTI from patients attendinga tertiary care hospital located in the North-East region of India. To gain a thorough understanding of its epidemiology, the study also examined several co-factors that contribute to GNB-induced UTI.

MATERIALS AND METHODS

Study design and setting

It is a retrospective cross-sectional study for a period of 3 years from January 2021 to December 2023 from patients suspected of UTI attending at Regional Institute of Medical Sciences, Imphal, India.The results of positive urine cultures with GNBfrom patients suspectedof UTIs, including age, sex, co-morbidity, month, source of sample (OPD, ICU and Ward), pathogen identification and antibioticsusceptibility testing were collected.

Sample collection

Urine samples were collected in accordance with Standard Operating Procedures (SOP) described by the Indian Council of Medical Research (ICMR), New Delhi, India [6]. Briefly, midstream clean catch urine was collected in a sterile, wide-mouthed, screw-capped container after very thorough preliminary cleaning.

Processing of samples

The samples were inoculated into blood agar and MacConkey agar after direct microscopy *viz.*, Gram's staining, acid-fast staining, and wet mount observation to rule out any other infection. The plates were further incubated at 37°C for 18 to 24 hours.

Identification of bacteria

Bacterial strains were isolated and identified phenotypically based on biochemical reactions. Furthermore, isolate identification was confirmed using the Vitek 2 compact system (BioMerieux Inc., France).

Antibiotic susceptibility testing (AST)

AST of the bacterial isolates were performed through Kirby-Bauer Disk Diffusion Susceptibility Test using Muller Hinton Agar. Antibiotics of different class in the panel namely aminoglycoside [amikacin (30µg), tobramycin, gentamicin (10µg)], cephalosporin [ceftriaxone (30µg), cefepime (30µg), cefazolin (30µg), ceftazidime (30µg), cefotaxime (30µg)], phosphonic [fosfomycin(200µg)], carbapenem [imipenem (10µg), meropenem (10µg), ertapenem (10µg)], nitrofuran (nitrofurantoin [300µg)], tetracycline [minocycline (30µg)], penicillins and beta-lactamase [piperacillin tazobactam (100/10 µg)], sulfonamide [trimethoprim-sulfamethoxazole(25µg)], fluoroquinolones [levofloxacin (5µg)] and quinolones [Ciprofloxacin(5µg)] were included. Interpretation of the AST was done according to guidelines from Clinical and Laboratory Standards Institute (CLSI) M100 30th ed., 2020 [7]. For quality control, *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) were included as the reference strains. The plates were incubated at 37^{o}C for 18 to 24 hours.

RESULTS

A total of 4333 urine samples were cultured positive for UTI with various GNB. The number of UTI cases was significantly higher during the year 2023 (51.1%, *n*=4333) compared to the previous years (2021 & 2022) (Table 1). The prevalence of UTIs was frequently observed in female patients in comparison to male patients during our study period.Interestingly, month-wise distribution of UTI observed that there is a rapid increase during July to October by, and this pattern is observed in the second yearand third year of the study period, recorded as the peak period. However, the maximum case was observed during October and December in the first year of the study (Table 2). Age factor study of UTI showed patients from the age group 51 to 70 years were more affected (Table 3), and elderly patients above 80 years old(4.1%, *n*=4333) were also affected; however, among the elderly group, males (60.5%, *n*=180) rather than females were more prone to UTI as observe in our study period and region. Children below 10 years are also affected (9.85%, *n*=4333), particularly female children. As observed,24.3% (*n*=4333) of the recorded patients were found to be in association with other underlying illnesses. The most common being diabetes mellitus (34.5%, *n*=1055), hypertension (28%, *n*=1055), and chronic kidney disease (24.1%, *n*=1055), among others, including acquired cystic kidney disease (ACKD), hepatitis, carcinoma, cerebrovascular accident (CVA), decompensated chronic liver disease (DCLD), myeloma, paraplegia, etc.

22 species from 12 different genera of GNB were found to be associated with UTI. Among the bacterial species, *E. coli*was the most frequently isolated bacteria in association with UTI patients with a prevalence rate of 60.8% (*n*=4333) (Table 1). *Klebsiella* sp. altogether accounted for 1025 (23.6%, *n*=4333) of which *K. pneumoniae* (17.3%, *n*=4333) is the most predominant among the species. *Pseudomonas aeruginosa* (5.07%, *n*=4333), *Acinetobacter baumannii* (3.04%, *n*=4333), and *Proteus mirabilis* (2.2%, *n*=4333) were also isolated and identified to be moderately associated with UTI patients. The less frequently encountered GNB in this study include *Salmonella typhi, Serratia marcescens*,

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Providencia rettgeri, *Aeromonas* sp., and *Burkholderiacepacia*.

49.4% (*n*=4333) of the culture-proven GNB causing UTIs are from OPD; despite this, *A. baumannii, K. pneumoniae,* and *P. aeruginosa* are predominantly isolated from ward patients (Table 1). *E. coli* was isolated as the most predominant GNB causing UTI among patients from the ICU, OPD, and ward. The study further looks into the correlation in the distribution of the pathogens against gender. A male preponderance with 52.2% (*n*=178), 71.3% (*n*=220), and 56.7% (*n*=141) was observed in *Acinetobacter* sp., *P. aeruginosa*, and *Proteus* sp., respectively. Interestingly, our study highlights the consistent presence of *Acinetobacter* sp., *P. aeruginosa,* and *Proteus* sp. among male patients in comparison to female UTI patients. Similarly, the pathogens distribution was correlated with month-wise distribution (Figure 1). *A. baumannii* and *E. coli* are more or less evenly distributed throughout the months.Nevertheless, non-*baumannii Acinetobacter* and *Citrobacter freundii*have higher incidence during August and September. *K. oxytoca*and *K. pneumoniae* were evenly distributedthroughout the months. Nevertheless, *K. aerogenes* and other species of *Klebsiella* have random distribution throughout the study period. Moreover, the aetiological agents are correlated with different age groups, which showed that *E. coli* and *K. pneumoniae* prevalence increases with an increase in age and declines as the age declines (Table 4).The highest incidence of *E. coli* and *P. aeruginosa* was observed among the age group of 51 to 60 years. Additionally, children below 10 years have significant culture positivity of *E. coli* (10.6%, *n*=2637), *K. oxytoca* (13.8%, *n*=239), and *K. pneumoniae* (7.4%, *n*=750) as recorded during our study period.

Overall, none of the tested antibiotics were 100% (*n*=4333) sensitive to the tested GNB (Figure 2). The highest sensitivity was observed from fosfomycin (87.9%, *n*=4333), followed by amikacin (81.3%). And the less sensitive antibiotics were ceftriaxone (5.8%, *n*=4333) and cefotaxime (8.4%, *n*=4333). Nitrofurantoin sensitivity was observed in 70.8% (*n*=4333) of the tested isolates. The antibiotics from the cephalosporin class have less activity toward the UTI pathogens. Among the carbapenems, meropenem (76.5%, *n*=4333) was more effective in comparison with ertapenem (56.6%, *n*=4333) and imipenem (46.02%, *n*=4333).Since *E. coli* and *Klebsiella* sp. represent 84.5% (*n*=4333) of the culture-proven UTIs in the present study, their antibiograms are analyzed extensively based on their source of isolation (ICU, OPD, and ward) (Figure 3). *E. coli* strains isolated from the ICU were shown to have higher resistance when compared to strains from OPD and ward (Table 5 and table 6). Amikacin resistance against *E. coli* was noted to be 26.3% (*n*=129), 5.7% (*n*=1473), and 12.5% (*n*=1035) from ICU, OPD, and ward, respectively. Among the carbapenems, a higher frequency of resistant *E. coli* from ICU was observed from ertapenem (61.1%, *n*=129) and imipenem (60.3%, *n*=129). Similarly, nitrofurantoin sensitivity against *E. coli* was found to be 69.8% (*n*=129), 83.5% (*n*=1473), and 82.8% (*n*=1035)from ICU, OPD, and ward, respectively. The least resistance was observed in fosfomycin, with resistance ranging from 5.5% (*n*=1473) to 9.3% (*n*=1035). Nevertheless, with respect to fosfomycin, *E. coli* isolated from the ward have a higher frequency of resistance (9.3%, *n*=1035).*Klebsiella* sp. showed a more or less similar pattern as that of *E. coli,* where strains isolated from ICU is more resistant to antibiotics. Compared to *E. coli*, *Klebsiella* sp. from ICU patients has more resistance to amikacin (57.2%, *n*=131). Similarly, the resistance range of fosfomycin for *Klebsiella* sp. is 14.6% (*n*=403) to 24.4% (*n*=131), which is comparatively higher than *E. coli*. Additionally, the sensitivity rate of *Klebsiella* sp. from ICU, OPD, and ward toward nitrofurantoin was 32.8% (*n*=131), 52.1% (*n*=403), and 45.6% (*n*=491), respectively.Among the *E. coli* and *Klebsiella* sp., 24.5% (*n*=3662) are susceptible strains, whereas 63.1% (*n*=3662) and 12.2% (*n*=3662) of the strains respectively are multidrug-resistant (MDR) and extensively drug-resistant (XDR), respectively (Table 7). No pan-antibiotic-resistant (PDR) *E. coli* or *Klebsiella* sp. were isolated in the study. In both cases of *E. coli* and *Klebsiella* sp., strains from ICU have a higher prevalence of XDR. In particular, *Klebsiella* sp. from ICU has a 54.1% (*n*=131) prevalence of XDR, which is more than double that of *E. coli* with 24.8%.

Table 1. GNB causing UTI and its distribution according to source wise, year wise and gender wise (*n*=4333).

Aetiology	Source wise			Year wise			Gender wise	
	ICU	OPD	Ward	2021	2022	2023	Female	Male
Acinetobacter baumannii	24	34	74	35	32	65	59	73
Acinetobacter lwoffii	-	19	16	1	9	25	21	14
Acinetobacter sp.	1	3	7	4	5	2	5	6
Aeromonas sp.	-	1	-	-	1	-	1	-
Burkholderiacepacia	1	-	1	1	-	1	-	2
Citrobacter freundii	4	14	20	7	13	18	18	20
Citrobacter koseri	3	26	18	-	24	23	24	23
Citrobacter sp.	-	1	2	-	2	1	1	2

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Enterobacter cloacae	1	3	4	3	5	-	4	4
Enterobacter sp.	-	7	7	3	1	10	8	6
Escherichia coli	129	1473	1035	441	864	1332	1750	887
Klebsiella aerogenes		5	16	1	17	3	11	10
Klebsiella oxytoca	29	97	113	5	87	147	136	103
Klebsiella pneumoniae	102	292	356	156	201	393	412	338
Klebsiella sp.	-	9	6	-	2	13	11	4
Morganella morganii	1	7	5	2	9	2	6	7
Proteus mirabilis	10	47	41	18	32	48	46	52
Proteus vulgaris	4	26	13	5	13	25	15	28
Providencia rettgeri	-	1	2	-	1	2	1	2
Pseudomonas aeruginosa	42	74	104	43	74	103	63	157
Salmonella typhi	-	1	-	1	-	-	-	1
Serratia marcescens	-	1	1	-	-	2	-	2
Total	**351**	**2141**	**1841**	**726**	**1392**	**2215**	**2592**	**1741**

Table 2. Month wise and corresponding year wise distribution of UTI pathogens.

Month	2021	2022	2023	Total
Jan	51	66	126	243
Feb	75	37	151	263
March	66	93	171	330
April	66	79	171	316
May	18	87	136	241
June	26	132	148	306
July	43	148	204	395
Aug	73	148	249	470
Sep	68	178	232	478
Oct	89	176	257	522
Nov	63	119	186	368
Dec	88	129	184	401
Total	**726**	**1392**	**2215**	**4333**

Table 3.Age wise and sex wise distribution of UTI pathogens.

Age group	Male	Female	Total
0-10	160	267	427
11-20	62	117	179
21-30	105	326	431
31-40	168	340	508
41-50	228	339	567
51-60	294	496	790
61-70	343	387	730
71-80	272	249	521
81 +	109	71	180
Total	**1741**	**2592**	**4333**

Table 4. Distribution of GNB causing UTI and its corresponding distribution according to age groups.

GNB	0 to 10	11 to 20	21 to 30	31 to 40	41 to 50	51 to 60	61 to 70	71 to 80	80 +	Total
Acinetobacter baumannii	16	7	15	16	16	16	22	16	8	132
Acinetobacter lwoffii	4	4	3	3	5	2	5	3	6	35
Acinetobacter sp.	1	-	1	1	1	3	3	1	-	11
Aeromonas sp.	-	-	-	1	-	-	-	-	-	1
Burkholderiacepacia	-	-	-	1	-	1	-	-	-	2
Citrobacter freundii	2	3	2	3	2	8	15	1	2	38
Citrobacter koseri	6	2	5	6	6	6	8	6	2	47
Citrobacter sp.	1	-	-	-	1	-	1	-	-	3
Enterobacter cloacae	-	1	2	2	2	-	1	-	-	8

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Enterobacter sp.	2	2	3	-	2	-	1	4	-	14
Escherichia coli	281	98	262	321	374	473	421	302	105	2637
Klebsiella aerogenes	3	2	3	1	-	3	-	3	6	21
Klebsiella oxytoca	33	13	21	23	22	47	44	29	7	239
Klebsiella pneumoniae	56	32	66	84	90	155	145	100	22	750
Klebsiella sp.	-	1	3	-	5	1	4	-	1	15
Morganella morganii	1	1	1	1		3	3	1	2	13
Proteus mirabilis	8	3	11	18	3	15	20	14	6	98
Proteus vulgaris	5	4	8	1	4	9	4	5	3	43
Providencia rettgeri	-	-	-	-	1	1	-	1	-	3
Pseudomonas aeruginosa	8	5	25	25	32	47	33	35	10	220
Salmonella typhi	-	1	-	-	-	-	-	-	-	1
Serratia marcescens	-	-	-	1	1	-	-	-	-	2
Total	**427**	**179**	**431**	**508**	**567**	**790**	**730**	**521**	**180**	**4333**

Table 5. Antibiogram of *E. coli* associated with UTI (*n*=2637).

Antibiotics	**ICU (*n*=129)**			**OPD (*n*=1472)**			**Ward (*n*=1035)**		
	R	**I**	**S**	**R**	**I**	**S**	**R**	**I**	**S**
Amikacin	34	8	87	84	71	1317	130	40	865
Cefazolin	123	5	1	1303	118	51	913	50	72
Cefotaxime	124	3	2	1311	48	113	941	28	66
Ceftazidime	115	12	2	1167	157	148	820	103	112
Ceftriaxone	114	9	6	1035	184	253	727	137	171
Ciprofloxacin	117	3	9	1068	216	188	826	97	112
Ertapenem	77	14	38	297	211	964	363	134	538
Fosfomycin	10	2	117	82	8	1382	97	9	929
Imipenem	76	17	36	427	328	717	368	164	485
Levofloxacin	112	6	11	879	180	413	735	100	200
Meropenem	60	7	62	221	149	1102	289	77	669
Minocycline	59	21	49	434	105	932	343	26	666
Nitrofurantoin	31	10	88	144	98	1230	120	57	858
Piperacillin Tazobactam	88	33	8	626	670	176	576	377	82
Trimethoprim-Sulfamethoxazole	90	4	35	737	26	709	597	10	428

R-Resistance, **I**-Intermediate, **S**-Sensitive

Table 6.Antibiogram of *Klebsiella* sp. associated with UTI (*n*=1025).

Antibiotics	**ICU (*n*=131)**			**OPD (*n*=403)**			**Ward (*n*=491)**		
	R	**I**	**S**	**R**	**I**	**S**	**R**	**I**	**S**
Amikacin	75	1	55	46	16	341	139	22	330
Cefazolin	122	6	3	338	41	24	412	47	32
Cefotaxime	129	0	2	316	31	56	435	14	42
Ceftazidime	117	3	11	276	38	89	383	39	81
Ceftriaxone	120	6	5	236	57	110	371	39	81
Ciprofloxacin	118	7	6	221	112	70	361	65	65
Ertapenem	91	7	33	119	55	229	238	48	205
Fosfomycin	32	4	95	59	18	326	103	29	359
Imipenem	86	11	34	139	78	186	228	69	194
Levofloxacin	109	6	16	175	75	153	301	63	127
Meropenem	75	13	43	82	55	266	192	48	251
Minocycline	54	12	65	91	42	270	164	49	278
Nitrofurantoin	78	8	45	146	47	210	229	38	224
Piperacillin Tazobactam	103	21	7	192	177	34	303	146	38
Trimethoprim-Sulfamethoxazole	87	3	41	180	8	215	270	9	208

R-Resistance, **I**-Intermediate, **S**-Sensitive

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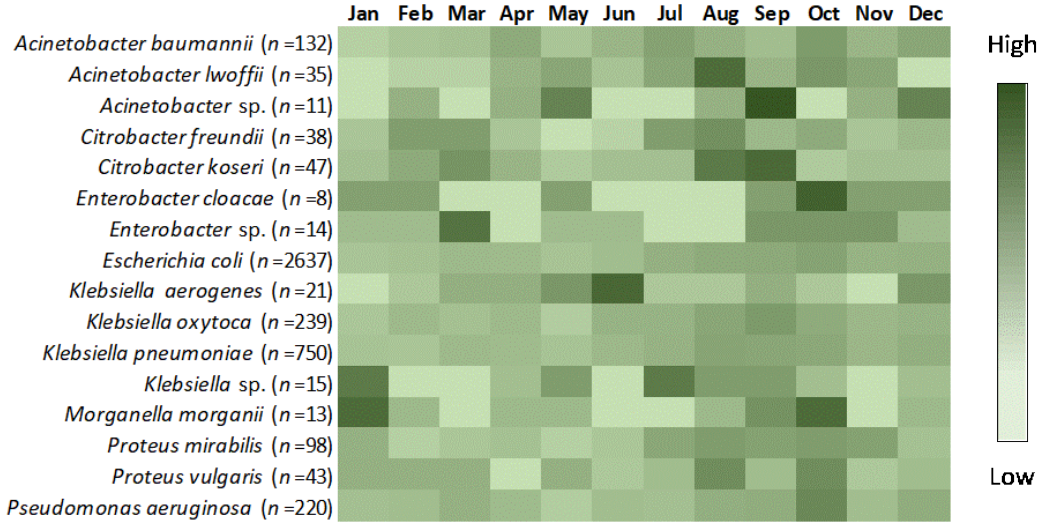
Table 7. Distribution of MDR, susceptible and XDR among *E. coli* and *Klebsiella* sp. associated with UTI.

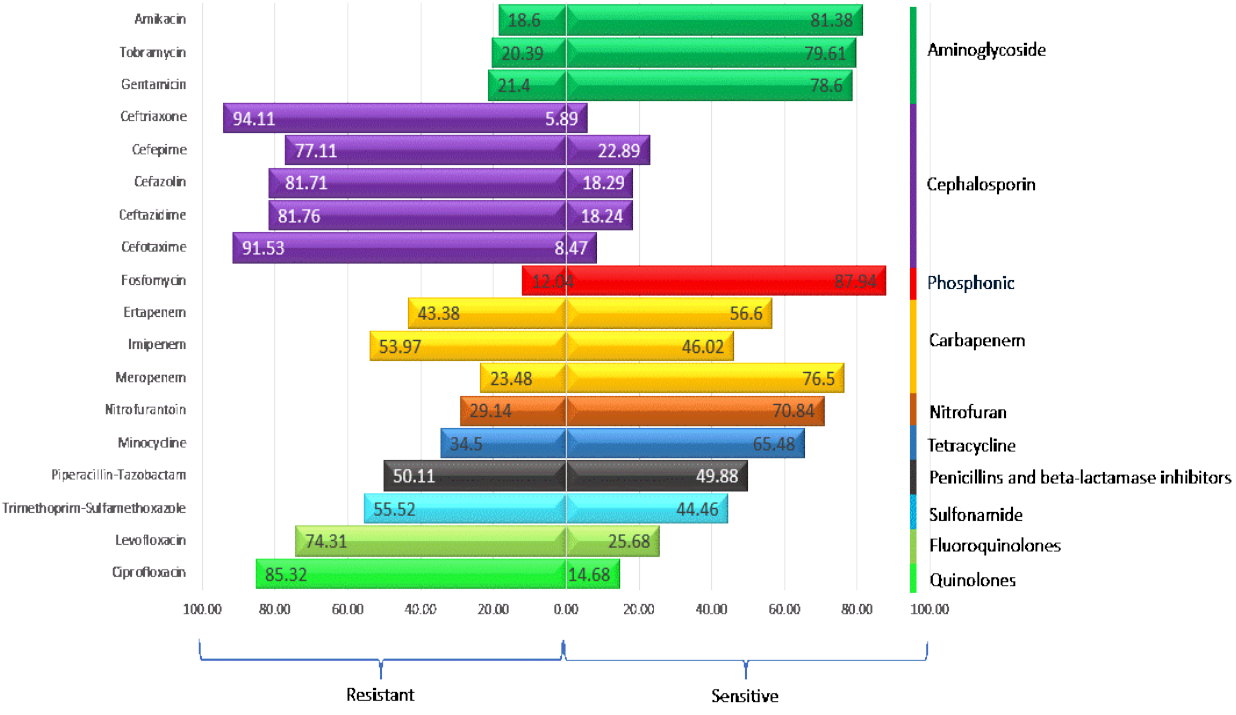
Antibiotic resistance	*E. coli* (*n*=2637)			*Klebsiella* sp. (*n*=1025)			Total
	ICU	OPD	Ward	ICU	OPD	Ward	
MDR	80 (62%)	995 (67.5%)	722 (69.7%)	58 (44.2%)	199 (49.3%)	259 (52.7%)	2313
SUSCEPTIBLE	17 (13.1%)	416 (28.2%)	229 (22.1%)	2 (1.5%)	146 (36.2%)	90 (18.3%)	900
XDR	32 (24.8%)	62 (4.2%)	84 (8.1%)	71 (54.1%)	58 (14.3%)	142 (28.9%)	449
Total	129	1473	1035	131	403	491	3662

Figure 1. Prevalence of gram-negative bacterial pathogens against month wise distribution.



The analysis does not include pathogens with $n \geq 3$. The heatmap displays the distributions of UTI pathogens wheredespite being isolated in greater quantities, *E. coli* did not exhibit a year-round peak occurrence or frequency. The distribution among the*Acinetobacter* sp. revealed that the frequencies varied with the months depending on the species.

Figure 2. Overall antibiotic susceptibility pattern of pathogenic gram-negative bacteria associated with UTI (*n*=4333).



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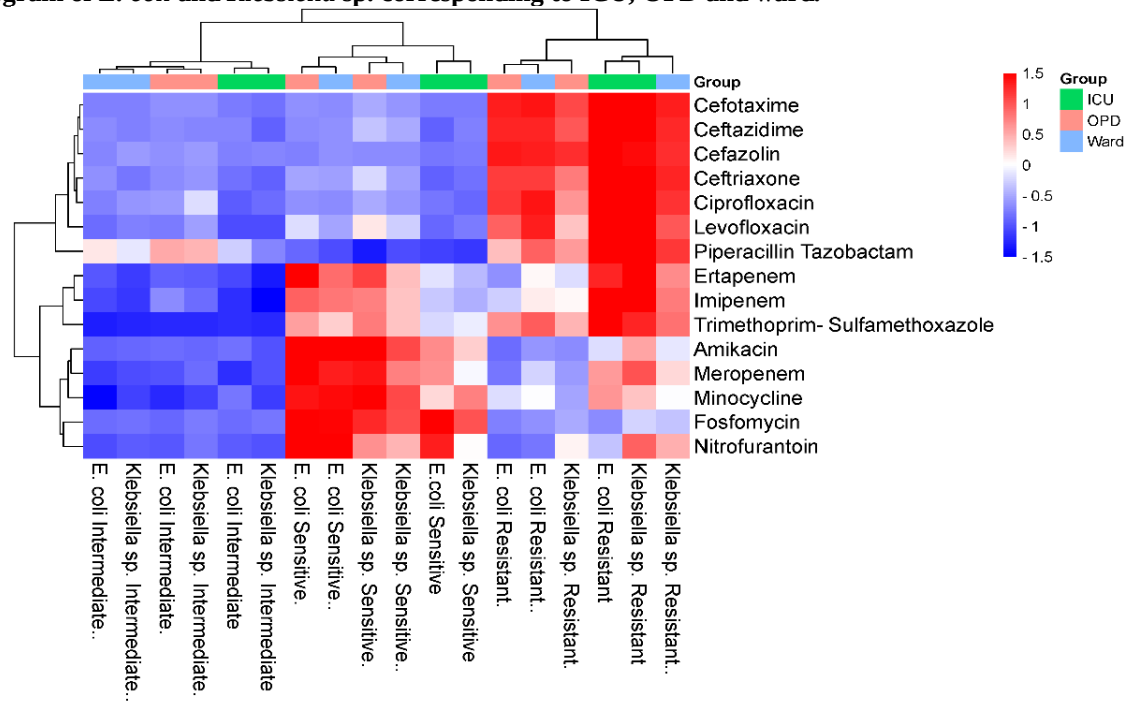
The figure shows the sensitivity of the tested antibiotics or according to its class of the antibiotics. Antibiotics in the phosphonic and aminoglycoside classes have been shown to be more sensitive to UTI bacteria. Antibiotics of the quinolone and cephalosporin classes demonstrated reduced susceptibilities to the GNB causing UTI.

Figure 3.Antibiogram of *E. coli* and *Klebsiella* sp. corresponding to ICU, OPD and ward.



A cluster heatmap demonstrating the high prevalence of resistance to cefotaxime, ceftazidime, cefazolin, ceftriaxone, ciprofloxacin, levofloxacin, piperacillin tazobactam, ertapenem, imipenem, and trimethoprim-sulfamethoxazole in *E. coli* and *Klebsiella* sp. isolated from ICU. Similarly, the sensitivity of amikacin, meropenem, minocycline, fosfomycin, and nitrofurantoin to *E. coli* isolated from the ICU and ward is higher.

DISCUSSION

Between 2021 and 2022, the frequency of UTIs increased by 91.7%, and between 2022 and 2023, the prevalence of UTIs increased by 59.1%. Interestingly, if we estimate from 2021 to 2023 we observe that there is a 205% increase in the prevalence of UTI in the study region. Numerous causes may have contributed to this concerning increase in UTIs, but the primary cause may be the rise in underlying illnesses like diabetes, post-COVID, cancer, etc. in this region. The current study found that July and October had higher rates of UTIs. The results are essentially consistent with earlier research showing that warmer temperatures raise the risk of UTIs [8,9]. Like earlier studies, a female majority of UTIs (59.8%, *n*=4333) was seen. Similar findings with female preponderance were reported with 60.7% [10], 63% [11]and 62.6% [9]. According to our research, people between the ages of 51 and 70 are more likely to get a UTI. However, research also found that women between the ages of 18 and 50 were more likely to get UTIs [11]. In congruence with our finding that elderly males are more prone to UTIs, Bhargava et al. (2022) reported that males over 80 years old were more susceptible than females [11]. 9.85% (*n*=4333) of the culture-proven UTIs are from children below 10 years of age, and within this group, females (62.5%, *n*=427) are more affected. UTI is more common in female and uncircumcised male infants, and the prevalence varies with age, peaking in young infants, toddlers, and older adolescents [12].Among the co-morbidity associated with UTI, diabetes mellitus is the leading underlying illness in the present study which is similar with recent studies[13,14]. Apart from diabetes mellitus, chronic kidney disease has been described as a risk factor for UTI[15]. Patients with diabetes often have increased complications of UTI, including rare complicationsemphysematous cystitis, pyelonephritis, fungal infections and increased severity and unusual manifestations.Previous reports suggestthat bacteriuria and urinary tract infection (UTI) occur more commonly in women with diabetes than in women without this disease[16].

E. coli (60.8%, *n*=4333) is the leading bacteria causing UTI, followed by *Klebsiella* sp. (23.6%, *n*=4333) and *P. aeruginosa* (5%, *n*=4333) in the present study. Literatures showed *E. coli* (47.97%), *K. pneumoniae* (24.58%), and *P. aeruginosa* (11.55%) from Saudi Arabia [9], *E. coli* (55.0%), *Proteus* sp. (6.9%) and *K. pneumoniae* (6.6%) from India [10], *E.*

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coli, *K. pneumoniae* and *P. mirabilis* from USA [5], *E. coli*, *K. pneumoniae* and *Enterococcus faecalis* from China [17] and *E. coli*, *Streptococcus agalactiae* and *P. mirabilis* from Brazil [18] as the pre dominants organisms for UTI. The results show *E. coli* is always the main aetiological agent of UTI; however, the second and third leading bacteria can vary from region to region. The dominating pathogens differ among the patients when categorically classified into ICU, OPD, and ward. Inclusively, *E. coli* was the predominant GNB causing UTI among patients from ICU, OPD, and ward. Nevertheless, pathogens such as *A. baumannii, K. pneumoniae*, and *P. aeruginosa* are predominantly isolated from ward patients when compared to OPD. A similar finding where *E. coli* is the predominant pathogen from OPD, inpatient, ICU, and emergency was reported [17]. The length of catheterization, and age (more than 60 years) were independent factors associated with the development of nosocomial UTI [19,20]. To reduce the risk of ICU-acquired UTIs, caution is crucial when working with patients in the intensive care unit.

Even though women are more affected by different GNBs, the current study shows that the distribution of these aetiologies differs by gender. *Acinetobacter* sp., *P. aeruginosa*, and *Proteus* sp. showed a male preponderance by 52.2% (*n*=178), 71.3% (*n*=220), and 56.7% (*n*=141), respectively.The current study could not ascertain the factors responsible for *Acinetobacter* sp., *P. aeruginosa*, and *Proteus* sp. dominance in males. Hence, further investigation is warranted. Understanding the seasonal distribution of UTIs can shed light on potential environmental and climatic influences, helping identify periods of heightened risk and enabling more proactive public health interventions [21]. The study recorded *A. baumannii* and *E. coli* are more or less evenly distributed throughout the month. A recent study revealed associations of UTI pathogens with the different seasons in which *E. faecium* demonstrated a substantial prevalence during the spring season, with 22.0% of isolates; *A. baumannii* displayed a notable association with the autumn season, accounting for 5.9% of isolates [11].The present study observed that not all UTI pathogens have the same pattern of month-wise or seasonal distribution. Some pathogens are distributed throughout the season, while some are more prevalent in a particular season. The study also observed that the frequency of UTI pathogens increases with an increase in age and declines as the age declines, particularly *E. coli* and *K. pneumoniae*. *E. coli* was the dominant UTI pathogen in children and adults in the present study, which agrees with a recent study from China [17].

It is well known that uropathogenic bacteria's susceptibility to antimicrobial drugs varies over time and between regions[22]. Depending on the source of isolation (ICU, OPD, or Ward), we found that the pattern of antibiotic susceptibility changes from strain to strain. In the ICU, OPD, and ward, *E. coli* resistance to amikacin was observed to be 26.3% (*n*=129), 5.7% (*n*=1473), and 12.5% (*n*=1035), respectively. It's interesting to note that *Klebsiella* sp. from the intensive care unit is more resistant to amikacin (57.2%, *n*=131). Cephalosporin showed the strongest resistance to the tested uropathogens. A 12-year retrospective study found that whereas *E. coli* had high ampicillin, sulfamethoxazole-trimethoprim, and cephalosporin resistance rates, *K. pneumoniae* had a greater resistance rate than *E. coli*[17]. Their findings are consistent with the current investigation, which demonstrates that *Klebsiella* sp. exhibits greater antibiotic resistance than *E. coli*. Furthermore, throughoutten years, a study found a noteworthy trend of rising cephalosporin resistance [23] as observed in our study.

According to Mahdizade et al. (2023), nitrofurantoin is thought to be the most effective medication for treating acute urinary infections. However, because of its long-term negative effects, particularly in older patients, it is crucial to establish certain criteria for prescribing nitrofurantoin in cases of chronic UTI [24]. Similar to a prior study of 80% sensitivity, nitrofurantoin demonstrated sensitivity in 70.8% (*n*=4333) of the uropathogens tested [25]. The ICU, OPD, and ward showed nitrofurantoin sensitivity against *E. coli* of 69.8% (*n*=129), 83.5% (*n*=1473), and 82.8% (*n*=1035), respectively. The sensitivity of *Klebsiella* sp. from ICU, OPD, and ward toward nitrofurantoin was 32.8% (*n*=131), 52.1% (*n*=403), and 45.6% (*n*=491), respectively. In congruence with the present finding, nitrofurantoin effectiveness against*E. coli* and *Klebsiella* sp. was 85% and 50%, respectively [14]. Nevertheless, a varying sensitivity, 49.7% of *E. coli*& 13.6% of *K. pneumoniae*[10], 53.2% of *E. coli*& 59.5% of *K. pneumoniae*[26], and 79.5% (*E. coli*) & 67.8% (*Klebsiella* sp.) [27] was documented. Nitrofurantoin is active against common causes of urinary tract infection, including *E. coli*, *Citrobacter*, and *Enterococcus. Klebsiella* sp. and *Enterobacter* sp. are, however, *Serratia* sp., *Acinetobacter* sp., *Morganella* sp., *Proteus* sp., and *Pseudomonas* sp. are usually resistant [27,28].

For patients with uncomplicated UTIs caused by resistant organisms, fosfomycin may be a viable therapy choice. For pregnant women with urinary tract infections, nitrofurantoin may be more effective [29]. In this investigation, fosfomycin showed the highest sensitivity (87.9%, *n*=4333) against the UTI bacteria. Fosfomycin sensitivity rates were 95.7% [30] and 98.0% [31] in essentially identical findings. It was found that up to 9.3% (*n*=1035) and 24.4% (*n*=131) of *E. coli*and*Klebsiella* sp. respectively were resistant to fosfomycin. Previous studies with the sensitivity of 77.9% (*E. coli*) & 80.8% (*K. pneumoniae*) [26]and 96% (*E. coli*) and 72.4% (*K. pneumoniae*) [32] were reported which is more or less similar to the present study.

75.4% (*n*=3662) of the *Klebsiella* sp. and *E. coli* are MDR/XDR in our study. 78.2% of the uropathogens

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were identified as MDR in a prior investigation [27]. Our investigation revealed that *E. coli* had a prevalence of 4.8% (*n*=3662) and 49% (*n*=3662)of XDR and MDR, respectively, whereas another study found that the most common instances of *E. coli* had both XDR (5.4%) and MDR (39.7%) [33]. All of the patients had a history of antibiotic exposure before they arrived at the studycentre, which is consistent with the high prevalence of MDR/XDR among *E. coli* and *Klebsiella* sp. It was suggested that the use of fluoroquinolones and antipseudomonal penicillins, as well as more cumulative days of treatment with any antimicrobial prior to UTI presentation, were most strongly associated with resistance (34,35).

The study has many limitations, including no follow up of the UTI cases is available. Epidemiological data describing socio-economic conditions of the patients, habitat (urban/rural) and geographical distribution of the patients could have brought more insight of the study.

CONCLUSION

The prevalence of UTIs in the region has increased in an alarming rate in the last two to three years. Even though*E. coli* is the most common GNB that causes UTIs, the major aetiological agent may vary depending on age, gender, health condition of the patient and season. As concluded, *Klebsiella* sp. hasa higher rate of antimicrobial resistance when compared to *E. coli* in our study period and region. Although the antibiotic susceptibility pattern varies by region, the source of isolation (ICU, OPD, or ward) and severity of the host patient may have an impact on the antimicrobial susceptibility pattern of the aetiological agent within a region. Strains originating from the ICU have more resistance frequencies.Given the severity of UTIs, the health authority can create a policy to combat the burden of UTIs. To reduce the prevalence of MDR and XDR, the study recommends a mandatory antibiogram profile before starting UTI treatment.

Data availability: All data supporting the findings of this study are available within the article.

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