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Emerging trends in uropathogens and their antibiogram with special reference to AmpC, Extended-spectrum β-lactamase and metallo-β-lactamase producers

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ABSTRACT

Urinary tract infections (UTIs) are among the most prevalent ailments in the Indian community. The susceptibility and spread of UTI-causing pathogens vary with time and location. This study aims to determine the frequency of UTI-causing microorganisms and the patterns of antibiotic sensitivity in patients from the Telangana region. This observational, prospective study was conducted over six months at a tertiary care hospital in Hyderabad, Telangana. A total of 105 clean-catch midstream urine samples were collected, and each specimen underwent Gram staining for microscopy. The isolates were then evaluated for the presence of urinary tract infections using standard culture techniques, biochemical reactions, and antibiotic susceptibility tests according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Extended-spectrum β-lactamase (ESBL), metallo-β-lactamase (MBL), and AmpC β-lactamase production were detected using double-disc synergy tests (DDST), imipenem-imipenem/EDTA disc tests, and disc-diffusion tests, respectively. Of the samples, 92.5% were identified as Gram-negative bacteria, while 7.5% were Gram-positive. The study observed a predominance of female patients (76.2%) compared to males (23.8%). Among the culture-positive samples, 62.5% were *Escherichia coli*, 22.5% were *Klebsiella pneumoniae*, and 7.5% were *Proteus mirabilis*. The prevalence of ESBL, AmpC, and MBL production was 20%, 7.5%, and 2.5%, respectively. In ESBL screening, *E. coli* showed the highest incidence (28%), followed by *K. pneumoniae* (11.1%). The antibiogram of *E. coli*, the predominant isolate, revealed the highest sensitivity to Amikacin (96%), Gentamicin (88%), Cefoxitin (88%), and Piperacillin-Tazobactam (84%), with lower sensitivity to Amoxicillin-Clavulanic Acid (56%) and Ampicillin (48%). The findings underscore a high prevalence of *E. coli* and *K. pneumoniae* among culture-positive samples. The study highlights the importance of identifying multidrug-resistant strains for effective therapy in bacterial infections, thereby reducing the risk of multidrug resistance in hospital and community settings.

Keywords: AmpC ß-lactamases, Beta-lactam, Drug resistance, ESBL, Urinary tract infections, Uropathogens

1. Introduction

Urinary tract infections (UTIs) are the common health problem that affects millions of people each year. Women are especially prone to UTIs. These are some of the most prevalent bacterial illnesses in healthcare. They affect all age groups, mostly women, due to anatomical variances. UTI epidemiology varies by region and population depending on age, gender, underlying health issues, and healthcare practices. Understanding the prevalent organisms causing UTIs and their antimicrobial resistance patterns is crucial for guiding appropriate empirical treatment and antimicrobial stewardship efforts. They are a very common health care problem presenting in community and nosocomial settings. According to the National Ambulatory Medical Care Survey, UTIs alone cause up to one million emergency department (ED) visits and over seven million Out Patient Department (OPD) visits, which leads to approximately 100,000 hospitalizations (Foxman 2003). Nearly 50–60% of women will experience a UTI at some point in their lives (ACOG practice bulletin 2008). It is also typical for UTI episodes to recur if the risk factors not promptly identified and addressed (Foxman et al., 2000). Serious side effects such as kidney damage, renal scarring, and renal failure can arise from an untreated UTI. Gram-negative bacteria such as *Escherichia coli, Proteus species, Pseudomonas aeruginosa, Acinetobacter species, Klebsiella species, Enterobacter species, and Citrobacter* species are the most common causes of UTIs. In gram-positive bacteria, *Staphylococcus saprophyticus, Enterococcus species,* and *Coagulase-negative Staphylococcus* are the common suspected spectrum of bacteria that are responsible for causing UTIs (Nguyen 2004, Momoh et al., 2011).

Antimicrobial resistance (AMR) and infectious diseases prevalence are major global health issues, specifically in developing nations like India. Other countries call India as the "AMR capital of the world" and is known for using antibiotics more than the rest of the world. Due to their higher frequency of multidrug resistance (MDR), gram-negative bacterial infections are significantly more dangerous than gram-positive bacterial infections (Veeraraghavan et al., 2019). Multidrug-resistant (MDR) organisms are those that show resistance to one agent in any three or more antibiotic classes. The number of MDR organism infections is continuously increasing, making it challenging to find effective treatment options. Data released by the World Health Organization (WHO) indicates that MDR infections have a significantly greater patient mortality rate than non-MDR organisms (Exner et al., 2017). As per the national pharmaceutical sales data from 2000 to 2010, India consumed about 10 units of antibiotics per person in 2010 alone, (Taneja et al., 2019). *Enterobacteriaceae* that is resistance to MDR is becoming one of the most substantial health issues in the world, which is causing treatment failure for nosocomial and community-acquired infections (Ghotaslou et al., 2018). One of the primary causes of bacterial resistance, which leads to the selection of various mutant forms of β-lactamases, is the inappropriate and unnecessary use of β-lactam drugs. The most concerning resistance mechanisms are extended-spectrum β-lactamases (ESBLs), AmpC, and metallo-β-lactamase (MBL), which have an unpredictable effect on antimicrobial chemotherapy. A type of β-lactamases known as ESBLs confers resistance to aztreonam, cephalosporins, and penicillins. While they are still vulnerable to cephamycins and carbapenems, they develop resistance by hydrolyzing these antibiotics. Additionally, β-lactamase inhibitors, such as clavulanic acid, can decrease their activity (Wadekar et al., 2013). In addition to β-lactam medications, ESBL-producing organisms are resistant to a number of different kinds of antimicrobial medicines, such as aminoglycosides, cotrimoxazole, tetracycline, and fluoroquinolones, (Wadekar et al., 2013). Cephalosporins, cephamycins, aminopenicillins, and monobactams can all be hydrolyzed and rendered inactive by AmpC β-lactamases, which are less susceptible to clavulanic acid (Chanu et al., 2019). Prior to the emergence of carbapenem-resistant bacteria, carbapenems were the only treatment available for infections that produced AmpC and ESBL. Thus, the future of antibiotics has been clouded by the rise of MBL producers. This global health security issue is exacerbated by carbapenem-resistant Enterobacteriaceae (CRE), which can spread with plasmids and are often associated with either ESBL, AmpC β-lactamase, or both (Mirza et al., 2019).

There is a lack of information on the detection of ESBL, AmpC, and MBL. One of India's Southern states, Telangana is 11th largest state and 12th most populated state in India. It is home to about 38.32 million people, with a higher proportion of rural areas and relatively poor medical facilities (Telangana social development report, 2017). It is crucial to identify and evaluate these β-lactamases in order to stop and manage the spread of infections and treat severe cases. Additionally, MDR infections are rapidly increasing in hospital settings due to the direct use of expanded-spectrum cephalosporins without appropriate control mechanisms. Considering this, the current study is to ascertain the frequency of UTI-causing microorganisms and the patterns of antibiotic sensitivity in patients who visit the departments of medicine, obstetrics and gynecology, and urology at Shadan Institute of Medical Sciences, in Hyderabad. Through phenotypic screening and confirmatory testing, this study also finds that the identified microbes produce ESBL, AmpC, and Metallo-beta-lactamase (MBL).

2. Materials and methods

It is an observational, prospective study of 6 months, conducted at Shadan Institute of Medical Sciences, Hyderabad, Telangana, by the Department of Microbiology, from July to December 2023. Ethical approval (EC/NEW/INST/2023/4198/RR-16) was taken before the initiation of the study. 105 midstream clean catch urine samples were collected from patients. Each specimen underwent Gram staining for microscopy before being inoculated onto blood agar (BA) and MacConkey agar (MA) plates (HiMedia Laboratories Pvt. Ltd., Mumbai, India) and incubated aerobically for 18 to 24 hours at 37°C. All isolates were then evaluated for the presence of urinary tract infection using standard culture, biochemical reactions, and antibiotic susceptibility for *Enterobacteriaceae* members.

Direct microscopy of urine samples with significant bacteriuria was further processed by doing a wet mount with normal saline to see pus cells, and a Gram stain was done to identify gram-positive and gram-negative bacteria. Samples are further inoculated by streak culture onto MA, BA, and NA plates to obtain individual colonies and incubated overnight. Individual colonies are identified and subjected to conventional biochemical tests like ICUT for gram-negative bacilli and catalase, coagulase, and heat tolerance tests for gram-positive cocci.

Antimicrobial Susceptibility Testing

Using the Kirby-Bauer disk diffusion method and Mueller-Hinton agar (MHA), all detected members of the *Enterobacteriaceae* were tested for antibiotic susceptibility in accordance with CLSI standards. Lawn culture using the 0.5 McFarland opacity standard of inoculum used. 6-8 antibiotic discs are placed in 100 mm MHA plates and incubated for 16-18 hrs. Zones of inhibition were measured after incubation with a ruler and interpreted as per CLSI guidelines. Penicillin, amoxicillin clavulanic acid, erythromycin, clindamycin, cotrimoxazole, ampicillin, nitrofurantoin, gentamicin, amikacin, cefotaxime, cefoxitin, ceftazidime, imipenem, piperacillin-tazobactam, and nitrofurantoin are the antibiotics used.

Extended spectrum β lactamase detection

Gram-negative isolates that exhibited resistance to at least one antibiotic in three or more antimicrobial categories were subjected to ESBL determination. Screening was done by cefotaxime resistance disc diffusion test. A zone of inhibition of ≤ 27 mm was indicative of potential ESBL production. Isolates showing resistance to cefotaxime were subjected to the double disc synergy test (DDST) for confirmation. In this test, discs containing cefotaxime and clavulanic acid (a beta-lactamase inhibitor) were placed 20 mm apart on a Mueller-Hinton agar plate by the lawn method and inoculated with the test organism. The test organism was regarded as an ESBL producer if the zone of inhibition around the combination disk was at least 5 mm larger than that of the cephalosporin alone.

AmpC detection test

AmpC beta-lactamase production was screened using cefoxitin discs in the disc diffusion method. A reduced zone of inhibition around the cefoxitin disc (≤ 18 mm) was suggested by the presence of AmpC beta-lactamases. For confirmation, the AmpC disc test was employed. In this test, a disc impregnated with a specific inhibitor for AmpC beta-lactamases was used. A significant increase in the zone of inhibition around the cefoxitin disc in the presence of the inhibitor was confirmed as AmpC production (Maraskolhe et al., 2014).

MBL detection test

MBL production was screened by detecting resistance to imipenem using the disc diffusion method. A reduced zone of inhibition around the imipenem disc (≤ 22 mm) was indicative of potential MBL production. For confirmation, the imipenem-EDTA combined disc test was performed. In this test, two discs containing imipenem were placed on a Mueller-Hinton agar plate inoculated with the test organism. One of the discs was supplemented with EDTA, a chelator that inhibits MBL activity. An increase in the zone of inhibition around the imipenem-EDTA disc compared to the imipenem-alone disc was confirmed as MBL production.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 20 was used to conduct the statistical data analysis. Descriptive statistics were computed, and data were presented using percentages.

4. Results

In the current study, a total of 105 samples were collected, out of which 40 were determined to be culture positive. Among the 40 samples, 92.5% (n=37) were identified as Gram-negative bacteria (*E. coli*, *K. pneumoniae* and *Proteus mirabilis*), while 7.5% (n=03) were identified as Gram-positive bacteria (*S. aureus* and *E. faecalis*) (Figure 1).

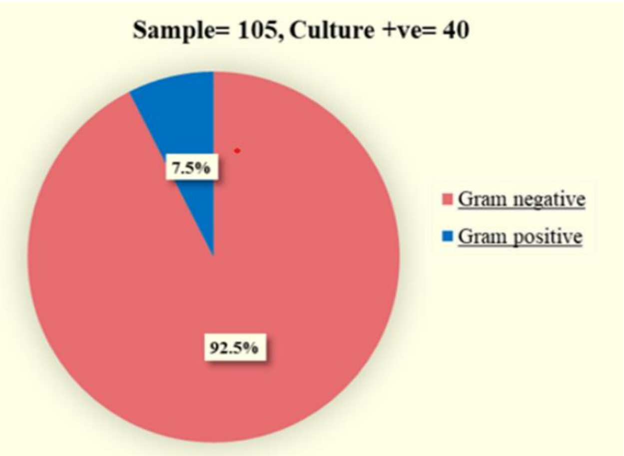
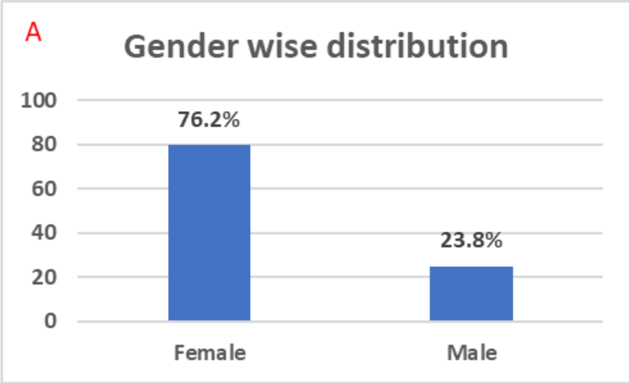


Fig 1. Percentage of gram bacterial distribution in urine samples

In Figure 2A, the gender-wise distribution of the overall sample shows that the female population was predominant with 76.2% (n=80) over males, who were 23.8% (n=25). A gender-wise comparison in culture-positive samples has shown that 75% of the population are females (n=30) and 25% are males (n=10) (Figure 2B).



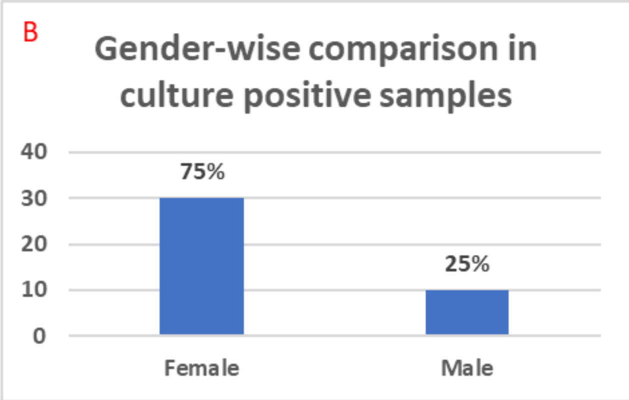


Fig. 2. Gender-wise distribution in overall samples and culture positive samples.

Overall, culture-positive results in Table 1 illustrate that *E. coli* (62.5%) was the predominant bacterial organism isolated, followed by *K. pneumoniae* (22.5%), *P. mirabilis* (7.5%), *S. aureus* (5%), and *E. faecalis* (2.5%).

Table 1. Bacteriological profile of culture positive samples.

	Name of the Bacteria	**No. of Isolates**
Gram -ve isolates	*Escherichia coli*	25 (62.5%)
	Klebsiella	9 (22.5%)
	Proteus mirabilis	3 (7.5%)
	Total	**37(92.5%)**
Gram +ve isolates	*Staphylococcus aureus*	2 (5%)
	Enterococcus faecalis	1 (2.5%)
	Total	**3 (7.5%)**

Abbreviations: -ve = Negative; No. = Number; +ve = Positive

Table 2 explained the prevalence of ESBL (20%), AmpC (7.5%), and MBL (2.5%) production in the study samples. Table 3 described the organism-wise distribution of isolates by phenotypic and confirmatory test. In the ESBL screening test, *E. coli* was found to be 28% (n=07) and *K. pneumoniae* was found to be 11.1% (n=01), and the results were confirmed by DDST (Figure 2A). *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 were used as control strains. The AmpC production screening test resulted in 12% (n=03) of *E. coli* bacteria, and the same was confirmed by the AmpC disc test (Figure 2B). MBL screening tests have shown 4% (n=01) *E. coli* bacteria, and the same was confirmed by *the imipenem*-EDTA combined disc test (Figure 2C).

Table 2. Prevalence of ESBL, MBL and Amp C

Resistance pattern	Prevalence of resistance n=37
ESBL	8 (20%)
MBL	1 (2.5%)
AmpC	3 (7.5%)

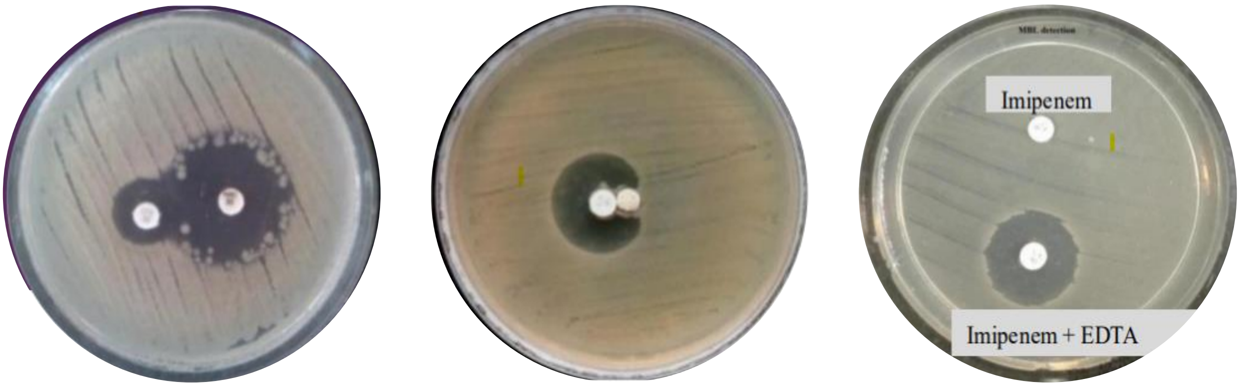
Abbreviations: AmpC = AmpC β-lactamases; ESBL = Emergence of extended-spectrum beta-lactamases; MBL = Metallo-β lactamases; N = Number of participants

Table 3. Organism wise prevalence of ESBL, MBL and AmpC in different isolates

Organism	ESBL	MBL	AmpC
E. coli	7(28.0%)	1(4.0%)	3 (12.0%)
K. pneumoniae	1 (11.1%)	-	-
Total	8	1	3

Abbreviations: AmpC = AmpC β-lactamases; ESBL = Emergence of extended-spectrum beta-lactamases; MBL = Metallo-β lactamases

Antibiogram of isolates showed 100% sensitivity to *S. aureus* (Table 4). Furthermore, penicillin, clindamycin, ampicillin, and nitrofurantoin antibiotics have shown 100% sensitivity to *E. faecalis*. The rest of the antibiotics have shown intermediate resistance (IR) in *E. faecalis*. For each susceptibility test, *K. pneumoniae* ATCC 700603 and *E. coli* ATCC 25922 were used as controls.



A. Double disc synergy test **B**. AmpC disc test **C**. Disc Diffusion test

Figure 2A, 2B, and 2C. Detection of ESBL, MBL, and Amp C.

Table 4: Antibiotic susceptibility pattern of *S. aureus* and *E. faecalis*

Antibiotics	Sensitivity to *S. aureus* (N=2) 5%	Sensitivity to *E. faecalis* (N=1) 2.5%
Penicillin	2 (100%)	1 (100%)
Amoxicillin clavulanic acid	2 (100%)	IR
Cefoxitin	2 (100%)	IR
Erythromycin	2 (100%)	IR
Clindamycin	2 (100%)	1 (100%)
Cotrimoxazole	2 (100%)	IR
Ampicillin	NA	1 (100%)
Nitrofurantoin	2 (100%)	1 (100%)

In the antibiogram of *E. coli,* which is a predominant isolate in the study, maximum sensitivity was shown for amikacin (96%), gentamicin (88%), cefoxitin (88%), and piperacillin-tazobactam (84%), followed by amoxicillin-clavulanic acid (56%) and ampicillin (48%). The least sensitive have shown towards Nitrofurantoin (20%). In the antibiogram of *K. pneumoniae,* which is the second predominant isolate in the study, with 100% sensitivity for amikacin and piperacillin-tazobactam, followed by gentamicin and cefoxitin (88.9%) with maximum sensitivity. And the least sensitivity was seen in amoxicillin-clavulanic acid (44.5%). Antibiogram of minor isolate *Proteus mirabilis* has shown 100% sensitivity with the majority of antibiotics and the IR with Nitrofurantoin.

Table 5. Antibiotic susceptibility pattern of *E. coli, k. pneumoniae,* and *P. mirabilis*

Antibiotics	Sensitivity to *E. coli* (N=25) 62.5%	Sensitivity to *K. pneumoniae* (N=9) 22.5%	Sensitivity to *P. mirabilis* (N=3) 7.5%
Ampicillin	12 (48%)	IR	3 (100%)
Gentamicin	22 (88%)	8 (88.9%)	3 (100%)
Amikacin	24 (96%)	9 (100%)	3 (100%)
Amoxicillin clavulanic acid	14 (56%)	4 (44.5%)	3 (100%)
Cefoxitin	22 (88%)	8 (88.9%)	3 (100%)
Cefotaxime	11 (44%)	5 (55.6%)	2 (66.7%)
Ceftazidime	9 (36%)	6 (66.7%)	3 (100%)
Imipenem	–	–	–
Piperacillin tazobactam	21 (84%)	9 (100%)	3 (100%)
Nitrofurantoin	8 (20%)	5 (55.6%)	IR

5. Discussion

The present study gives data for identifying and comparing the antimicrobial resistance state in uropathogens to develop effective empirical treatment. Of the 105 samples obtained, 40 were culture-positive. The prevalence of UTI in the present study from 40 samples (38.09%) is greater compared to the other research, which accounts for 25.6% (Nedolisa 1998), 22% (Ekweozor et al., 1996), and 4.2% (Bigwan et al., 2013) in India. Aftereffects of COVID-19 in some people experience prolonged symptoms like a weaker immune system, fatigue, respiratory infection, and shortness of breath. From 40 culture-positive samples in the present study, a suspected reason could be a weaker immune system, which is prone to causing UTIs in Telangana state. Women patients with UTIs are higher in number (76.2%), which is consistent with a previous study (Sood et al., 2012). The reasons for high females being prone to UTIs could be because of a shorter urethra, close proximity of the urethral meatus to the anus, and poor hygiene habits (Orrett et al., 2006).

The data shown in Table 1 illustrates that the gram-negative bacilli are 92.5% out of total isolates, whereas gram-positive were 7.5%. The most common gram-negative bacterium in the urine samples that tested positive for UTI was *E. coli* (62.5%). These results are consistent with other research findings but vary from the research in which *P. aeruginosa (*Ehinmidu et al., 2003) and *Klebsiella* spp. (Aboderin et al., 2009) were the predominant organisms in UTI. Along with the E. coli, *K. pneumoniae (22.5%) and P. mirabilis*. (7.5%) are the other isolates that are the second and third predominant bacteria. These findings are consistent with recent studies that found Klebsiella spp. to be the second most isolated bacteria in UTIs (Abubakar 2009).

Research on UTIs in different parts of the world says that *E. Coli* and *Klebsiella* are the most predominant uropathogens in UTIs (Selvakumar et al., 2007). Various reasons for this are that the *Enterobacteriaceae* family is able to colonize easily in the urogenital mucosa with pili, adhesins, type 1 fimbriae, and P-1 blood group phenotype receptors (Das et al., 2006) and adhere to the uroepithelium. Out of 37 gram-negative samples in table 2, 20% are ESBL isolates, 7.5% are AmpC, and 2.5% are MBL producers, which are the prevalence of resistance. The most frequent producers were *E. coli* and *K. pneumoniae*. The above results indicate that the *Enterobacteriaceae* family members are the notorious bacteria that cause hospital- as well as community-acquired infections. This condition becomes a major risk factor for the spread of diseases (van Duin et al., 2016), and the disease condition gets worse if detected late and if not treated on time (Shankar et al., 2019).

In the present study, table 3 indicates that the maximum percentage of ESBLs in *E. coli* is 28.0%, followed by *K. pneumoniae* (11.1%). The data is lesser compared to the study by Metri et al. (2012). While in this study, ESBL producers were found to be 39.1% (8/37), this is in line with the Taneja et al. (2008) research with 36.5% ESBL production and contrasts with earlier study revealed 28.26% of uropathogens were ESBL positive (Gharavi et al., 2021). The second predominant isolate, *K. pneumoniae,* had lower ESBL production rates (11.1%) compared to *E. coli* (28%). A previous comparative analysis by Bharara et al. (2018) in India found a higher ESBL production *of E. coli* compared to *K. pneumoniae,* which is similar to the present study. ESBL detection rates in leading hospitals in India range from 19% to 60% (Bhattacharya, 2011). The prevalence of MBL seems to be 2.5% and is confirmed by the disc diffusion method; however, a high percentage of MBL in gram-negative bacteria was seen in *E. coli* (4.0%), which is similar to Amatullah et al. (2017) study. Similarly, the prevalence of AmpC was 7.5% and confirmed by the cefotaxime double disc synergy method. The production of AmpC was found in 12% of isolates in the present study, which is comparable with Sara et al. (2017) and lower than Shivanna et al. (2017) study.

Antibiotic susceptibility of the present study was more sensitive for gentamicin, amikacin, cefoxitin, piperacillin, and tazobactam drugs over the other isolated uropathogens. The sensitivity rates are observed that *E. coli* have Genta; 88%, Amika; 96%, Cefox; 88%, and Piper; 84%. *K. pneumonia* has Genta; 88.9%, Amika; 100%, Cefox; 88.9%, and Piper; 100%, and *Proteus mirabilis*. Have Genta; 100%, Amika; 100%, Cefox; 100%, and Piper; 100%. These results have shown similarity with the study done by Amatullah et al. (2017). Decrease in susceptibility is because of unrestricted use of antibiotics and highly prescribing practice of antibiotics by clinicians, which is a primary reason for antibiotic resistance (Kahlmeter 2003, Goettsch et al., 2000, Goossens et al., 2005). This advocates that many of the organisms develop ESBLs (Rodríguez-Baño et al., 2004).

Another theory for this condition is that third-generation cephalosporins are highly marketed and must have been vastly misused. As a result, microorganisms are evolving with various types of resistance mechanisms and have been showing altered modes of action to drugs. Immuno-suppression, poor hygiene, inappropriate use of broad-spectrum antibiotics, and prolonged hospitalization are other important etiological factors that raise the incidence of MDR infections (Manjunath et al., 2011). To overcome this scenario and avoid treatment failures, MDR organisms should always be tested and treated with the proper antibiotics once identified. Infections brought on by various β-lactamase pathogens, especially *Enterobacteriaceae*, can be lethal because there are no precise standards to identify the onset of β-lactamases. The current antimicrobial resistance dilemma could worsen because of inappropriate antibiotic administration (Khanna et al., 2016).

The high MDR rate observed in such a remote and thinly inhabited place highlights a peak of hazard in India's bigger towns. During the present COVID-19 pandemic, people may use antibiotics on their own out of fear or ignorance; this could be a sign of a more concerning elevated pattern of antibiotic resistance in India. Despite being more reliable and accurate, molecular techniques are too costly for a typical scenario in developing countries such as India. However, these phenotypic assays are more reliable and cost-effective, faster, and easier to get regularly and can identify a range of β-lactamases under simple laboratory conditions. In any basic laboratory setting, these phenotypic approaches can be utilized to screen, report, and record data for the presence of these β-lactamases at a lower cost in diverse rural parts of India.

Conclusion

In conclusion, the frequency of UTIs and the pattern of antibiotic resistance differed from region to region. Additionally, the prevalence of ESBL, MBL and AmpC β lactamases differed by location. In various reports, prevalence range was seen to be 0 to 100%. The increased use of third-generation cephalosporin medicines in clinical practice is another factor influencing the predominance of gram-negative bacteria. Therefore, a continuous monitoring is essential along with careful use of implicated antibiotics.

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