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Multi-drug Resistance and Extended-Spectrum β-Lactamase Production in Uropathogens from Hospitalized Patients in Gurugram, India

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A B S T R A C T

Urinary tract infections (UTI) are one of the most frequent problems in hospitalized patients. Infections caused by the gram-negative bacteria which produces Extended-spectrum β-lactamases (ESBL) have become the severe problem in the hospitals across the globe. Increase in extended-spectrum beta-lactamase producing organisms in recent years has led to the limitation of treatment option. This study was designed to evaluate the occurrence of different uropathogens producing ESBL, its antibiogram and Multi-drug resistance (MDR) status in hospitalized patients. 885 non-repetitive urine samples were collected in the study. A total of 293 (33.11%) samples showed significant bacteriuria. Females were found to be more infected as compared to males. The senior citizens were found to be most affected (>60 years). The most common ESBL producing uropathogens were *Escherichia coli* (*E. coli)* followed by *Klebsiella pneumoniae (K. pneumoniae).* All the ESBL positive isolates were found to be MDR. The prevalence of MDR was also significantly increased due to ESBL production. The monitoring of antibiotic resistance and susceptibility of bacterial strains should be mandatory due to the higher frequency of the ESBL producing uropathogens found in the hospitalized patients. It was proved in this study that the multi-drug resistance was responsible for the significant treatment failure. Hence testing of ESBL production in the uropathogens is warranted. It is also suggested not to prescribe any antibiotics without undertaking the culture and sensitivity report as it may further erode the antibiotics sensitivity in the studied regional population.

Introduction

UTIs are one of the most frequent problems in hospitalized patients[1]. Infections caused by the gram-negative bacteria which produces ESBL have become the severe problem in the hospitals across the globe. About 400 different types of ESBLs have been found around the world, among which TEM and SHV were more prevalent[2]. Mutations occurring in the genes encoding these enzymes are responsible for the formation of ESBLs[3].

Globally, the outbreaks of infection in various hospitals have been supplanting by endemicity of ESBL producing strains. This may lead to increased patient mortality when antibiotics inactive against ESBL-producers are used[4]. ESBL producing organisms are those that hydrolyse the oxyimino beta-lactams and monobactams but have no effect on the cephamycins and carbapenems. Cephalosporins have been used for the treatment of Gram-negative bacterial infections since 1980's[5]. Unfortunately, nowadays, beta-lactamase resistance has been growing among members of Enterobacteriaceae, including *E. coli* and *K. pneumoniae*. The most frequent cause of beta-lactam resistance is beta-lactamase enzymes, which disable beta-lactam drugs by breaking down the beta-lactam ring[6]. *K. pneumoniae* are the opportunistic pathogenic organism responsible for the different infections such as pneumoniae, UTIs and septicemia in both hospitalized and community environments[7]. Beta-lactams drugs which have a beta-lactam ring in their composition are used rampantly to save the lives of the patients with bacterial diseases[8].

Resistant bacteria are emerging across the world as a threat to favourable outcomes of treatment of common infections in the community as well as hospital-acquired infections. Urinary tract, pyogenic infections, respiratory infections and gastrointestinal infection are the most common infections caused by a family of Enterobacteriaceae. Among this family, *E. coli* has been the most commonly isolated pathogen. It is very well known to exhibit multidrug resistance. Prolonged or undesirable antibiotic therapy, overstay in the hospitals and nursing homes, severe illness, unlimited use of third-generation cephalosporins, fluoroquinolones, and increased use catheters are crucial risk factors for infections with MDR resistant *Escherichia coli*[9].

It is essential to understand that there may be the marked differences in the antibiogram between different geographic locations within the big country like India. Since most of the UTIs treated empirically, the selection of the antibiotics should be determined, not only by the predicted sensitivity profile. Thus, the knowledge of the local antibiogram of the common uropathogens is essential for the prudent empiric therapy. Therefore, with the reports on the high frequency of MDR and ESBL formation amongst the *E. coli* from different part of the India[9,10] and the paucity of information on their antibiogram, especially of the uropathogens from Gurugram-Haryana, an northern region in India, the present study was done to characterize the uropathogenic *E. coli* and *K. pneumoniae* which were circulating in this area with respect to the antibiogram. The prevalence of potential ESBL and MDR isolates were also explored.

Materials and Methods

Study design and area

This prospective study was conducted from urine samples collected from hospitalized patients complaining about UTIs. The samples were processed in Bacteriology Section, Department of Microbiology, Modern Diagnostic AND Research Centre, Gurugram, Haryana-India.

Processing of the samples

All samples were processed within 1-2 hours of the collection, and in case of delay, the specimens were refrigerated at 4ºC. All urine samples were cultured by the semi-quantitative method. In short, 0.01 ml of urine was inoculated on Cysteine lactose electrolyte deficient agar (CLED Agar) (Hi-media Pvt. Ltd) by crisscross streaking using disposable calibrated flexi-loop (Hi-media Pvt. Ltd) and incubated for 18-24 hours at 37^0C under aerobic conditions.

A pure growth of the gram-negative isolate on a colony count $\geq 10^5$ colony forming units was considered as significant bacteriuria. Isolation and identification of the strains were done following their morphology in Gram's staining, culture characteristics and biochemical properties. Plates with no growth were further incubated for another 24 hours before interpreting it as a negative culture.

Quality control

The bacterial suspension was prepared and was adjusted to a 0.5 McFarland standard solution (Hi-media Pvt. Ltd). American Type Culture Collection (ATCC) standard reference strains *P. aeruginosa* ATCC-27853, *S.aureus* ATCC-25923, *E. coli* ATCC-25922 were used as a quality control strains for antimicrobial susceptibility testing. All the ATCC strains used in the current prospective study were procured from Microbiologics, USA.

Antibiotic sensitivity testing

Antibiotic sensitivity testing was done by Kirby-Bauer disc diffusion method on Mueller-Hinton agar, and interpretation of the results was done as described by CLSI guidelines[11].

Antibiotics discs (Hi-Media Lab Pvt. Ltd) used were Ampicillin (AMP)-10 µg, Gentamicin (GEN)-10 µg, Tobramycin (TOB)-10 µg, Amikacin (AK)-10 µg, Amoxicillin-Clavulanic Acid (AMC)-20/10 µg, Ampicillin/Sulbactum (A/S)-20/10 µg, Piperacillin/Tazobactum (P/T)-100/10 µg, Cefuroxime (CXM)-30 µg, Cefepime (CPM)-30 µg, Ceftazidime (CAZ)-30 µg, Aztreonam (AT)-15 µg, Cefoxitin (CX)-30 µg, Levofloxacin (LE)- 5 µg, Ciprofloxacin (CIP)-5 µg, Imipenem (IMP)-10 µg, Ertapenem (ETP)-10 µg, Cotrimoxazole (COT)-25 µg, Tetracycline (TET)-30 µg, Nitrofurantoin (NIT)-300 µg.

Screening test for ESBL Production[17]

The organism was swabbed onto the Mueller Hinton agar (MHA) plate. Antibiotic discs Ceftazidime with zone diameter of ≤22 mm and Cefotaxime with zone diameter of ≤27 mm was considered indicative of suspicious for ESBL producer. These isolates were further subjected to the phenotypic confirmation testing[11].

Confirmatory test for ESBL production[17]

ESBL productions among the potential ESBL-producing strains by screening method were confirmed by CLSI phenotypic confirmation method. Comparison of the zone of inhibition was made for the Ceftazidime (30 µg) and Cefotaxime (30 µg), discs alone with the Ceftazidime and Cefotaxime discs containing Clavulanic acid (10 µg), ESBL production was confirmed by a >5mm increase in the zone diameter for either antibiotic tested in combination with Clavulanic acid against the zone diameter when tested alone confirmed the presence of ESBL production by that organism[11].

The increase in zone diameter was due to the inhibition of the β-lactamase by Clavulanate. *K. pneumoniae* (ATCC-700603) was used as a positive control, and *E. coli* (ATCC-25922) was used as a negative control.

Statistical analysis

Chi-square test was used for statistical analysis of the data. A p-Value of less than 0.05 was considered as statistical significant.

Results and Discussion

Demographical features of the studied subjects

In the current study, 885 urine samples suspected of urinary tract infection were collected in sterile and leak-proof containers from hospitalized patients in and around Gurugram, Haryana. The median age was 54 years, and the age range was 0-92 years. There were 66.89% (592/885) culture-negative samples, with the median age of 52 years and age range of 0-92 years. In the present study, 33.11% (293/885) samples were found positive for urine culture with the median age of 58 years and age range of 0-88 years. Prevalence of urinary tract infection among the age wise distribution showed a significant difference (p= 0.008) (Table 1). There were 52.43% (464/885) males included in this study and 79.74% (370/464) individuals presented with the negative urine culture. Rest of the 20.26% (94/464) males was presented with the positive urine culture. There were 47.57% (421/885) females included in the study and 52.73% (222/421) individuals presented with the negative urine culture. Rest of the 47.27% (199/421) females shown with the positive urine culture. Prevalence of urinary tract infection among the different gender showed a significant difference (p= 0.000) (Table 1).

ESBL status of the uropathogens

In the present study, Detection of ESBL was done by CLSI screening test followed by confirmatory tests[11]. It was performed for *E. coli*, *K. pneumoniae* and *Proteus mirabilis (P. mirabilis).* Among these, only *E. coli* and *K. pneumoniae* were found to be positive. A total number of 237 gram-negative bacteria (Median age: 59; Range: 0-88) were isolated. Among them, 20.25% (48/237) were ESBL producers (Median age: 58; Range: 0-80). and 43.88% (104/237) were non ESBL producers (Median age: 60 ; Range: 0-87) and 35.86% (85/237) were others isolates (Median age: 59; Range: 1-88). 44.73% (106/237) *E. coli* were isolated. The frequency of ESBL positive isolates was 35.85% (38/106), and ESBL negative isolates were 64.15% (68/106). 18.14% (43/237) *K. pneumoniae* were isolated. The frequency of ESBL positive isolates were 23.26% (10/43), and ESBL negative isolates were 76.74% (33/43). 1.27% (3/237). Interestingly, all the *P. mirabilis* isolates were ESBL negative (3,100%). In the current study, the frequency of ESBL negative uropathogens were significantly higher than ESBL positive strains (p= 0.046). Other GNB's were not tested for ESBL production (Table 2). There were 34.18% (81/237) males, in which 17.28% (14/81) isolates were ESBL positive, 37.04% (30/81) were ESBL negative and other GNB for which ESBL production was not tested were 45.68% (37/81). In females 65.82% (156/237), 21.79% (34/156) isolates were ESBL positive, 47.44% (74/156) were ESBL negative, and other GNB for which ESBL production was not tested were 30.77% (48/156). Prevalence of ESBL production among the genders distribution was showed no significant difference (p= 0.076) (Table 2).

Multidrug resistance patterns of ESBL +Ve/-Ve *E. coli* and *K. pneumoniae*

All the ESBL producing isolates were 100% resistant to all penicillin's, third-generation cephalosporins (e.g. ceftazidime, cefotaxime, and ceftriaxone) and Aztreonam. In ESBL positive *E. coli* (n=38), the most sensitive drug were Imipenem (97.0%), Ertapenem (95.0%), Nitrofurantoin (89.0%) and Amikacin (82.0%) and most resistant drugs Levofloxacin, Ciprofloxacin (97.0% each), Tetracycline,

Tobramycin, Ampicillin/Sulbactam (82.0% each), Cotrimoxazole (79.0%) and Gentamicin (55.0%) (Figure 1). In ESBL positive *K. pneumoniae* (n=10), the most sensitive drugs were Imipenem (100.0%), Cefoxitin (90.0%), Ertapenem (80.0%), Tetracycline (50.0%), and resistant to Cotrimoxazole, Ampicillin/ Sulbactam (90.0% each), Ciprofloxacin, Tobramycin (80.0% each) and Gentamicin (70.0%) (Figure 2). In ESBL negative *E. coli* (n=68) isolated from hospitalized patients, the most sensitive drug were Imipenem (81.0%), Ertapenem (78.00%), Amikacin, Nitrofurantoin (74.0% each) and resistant to Ciprofloxacin (82.0%), Levofloxacin (81.0%), Ampicillin (76.0%), Ampicillin/Sulbactam (65.0%) (Figure 1). In ESBL negative *K. pneumoniae* (n=33), the strain was sensitive to Imipenem (45.0%), Cefoxitin (39.0%), Amikacin Piperacillin/Tazobactam, Tetracycline (36.0% each), Amoxicillin/ clavulanic acid, Cefepime, Ceftazidime, Cefuroxime, Gentamicin, Levofloxacin, Nitrofurantoin, Tobramycin (30.0% each) and Resistant to Ampicillin (100.0%), Cotrimoxazole (73.0%), Ampicillin/ Sulbactam, Cefepime, Aztreonam, Ceftazidime, Cefuroxime, Ciprofloxacin, Gentamicin, Levofloxacin, Tobramycin (70.0% each), Amoxicillin/clavulanic acid (64.0%) (Figure 2). The sensitivity and resistance patterns of other antibiotics are showed in Figure 1 and 2.

In the current study, MDR was 82.55% (123/149), and Non-MDR was 17.45 % (26/149). The frequency of *E. coli* isolates were 71.14% (106/149), and *K. pneumoniae* were 28.86% (43/149). Among the 149 isolates, 32.21% (48/149) were ESBL positive, and 67.79% (101/149) were ESBL negative. There were 84.91% (90/106) were MDR *E. coli*, and 15.09% (16/106) were non-MDR *E. coli*. There were 76.74% (33/43) MDR *K. pneumoniae,* and 23.26% (10/43) were non-MDR *K. pneumoniae*. In ESBL positive group 79.17% (38/48) were *E. coli* and 20.83% (10/48) were *K. pneumoniae*. ESBL positive *E. coli* and *K. pneumoniae* were found as MDR (100%). In ESBL negative group, 67.33% (68/101) were *E. coli* and 32.67% (33/101) were *K. pneumoniae*. 76.47% (52/68) *E. coli* strains were MDR and 23.53% (16/68) were non-MDR. 69.70% (23/33) *K. pneumoniae* strains were MDR, and 30.30% (10/33) were non-MDR (Table 3).

Table.1 Demographical features of the studies subjects

Features	TOTAL (n)	Neg* (%)	Pos** (%)	*p-Value*
	885	592 (66.89	293 (33.11)	**NA**[#]
MEDIAN AGE (RANGE)	54 (0-92)	52 (0-92)	58 (0-88)	
AGE GROUP				
0-15	77 (8.70)	50 (64.94)	27 (35.06)	
16-30	135 (15.25)	106 (78.52)	29 (21.48)	**0.008**
31-45	135 (15.25)	97 (71.85)	38 (28.15)	
46-60	201 (22.71)	129 (64.18)	72 (35.82)	
>60	337 (38.08)	210 (62.31)	127 (37.69)	
GENDER				
MALE	464 (52.43)	370 (79.74)	94 (20.26)	**0.000**
FEMALE	421 (47.57)	222 (52.73)	199 (47.27)	

*Neg- Negative, **Pos- Positive, [#]NA – Not applicable

Table.2 ESBL Status of Studied Uropathogens from hospitalized patients

Features	Total GNB	ESBL+ve (%)	ESBL-ve (%)	Other GNB* (%)	*p-Value*
	237	48 (20.25)	104 (43.88)	85 (35.86)	NA#
MEDIAN AGE (RANGE)	59 (0-88)	58 (0-80)	60 (0-87)	59 (1-88)	
ORGANISMS					
E. coli	106 (44.73)	38 (35.85)	68 (64.15)	NA#	**0.046**
K. pneumoniae	43 (18.14)	10 (23.26)	33 (76.74)		
P.mirabilis	3 (1.27)	0 (0)	3 (100.0)		
K.oxytoca	**NF****	**NF****	**NF****		
Others	85 (35.86)	**NA#**	**NA#**		
GENDER					
MALE	81 (34.18)	14 (17.28)	30 (37.04)	37 (45.68)	0.076
FEMALE	156 (65.82)	34 (21.79)	74 (47.44)	48 (30.77)	

*GNB- Gram Negative Bacteria, #NA – Not applicable, NF**- Not found

Table.3 MDR Status of ESBL +/-ve *E. coli* and *K. pneumoniae* isolates from hospitalized patients

Features	Total (%)	MDR* (%)	NON-MDR* (%)
ORGANISMS	149	123 (82.55)	26 (17.45)
E. coli	106 (71.14)	90 (84.91)	16 (15.09)
K. pneumoniae	43 (28.86)	33 (76.74)	10 (23.26)
ESBL POSITIVE	**48 (32.21)**	**48 (100.0)**	**0 (0)**
E. coli	38 (79.17)	38 (100.0)	0 (0)
K. pneumoniae	10 (20.83)	10 (100.0)	0 (0)
ESBL NEGATIVE	**101 (67.79)**	**75 (74.26)**	**26 (25.74)**
E. coli	68 (67.33)	52 (76.47)	16 (23.53)
K. pneumoniae	33 (32.67)	23 (69.70)	10 (30.30)

*MDR- Multi-Drug Resistant.

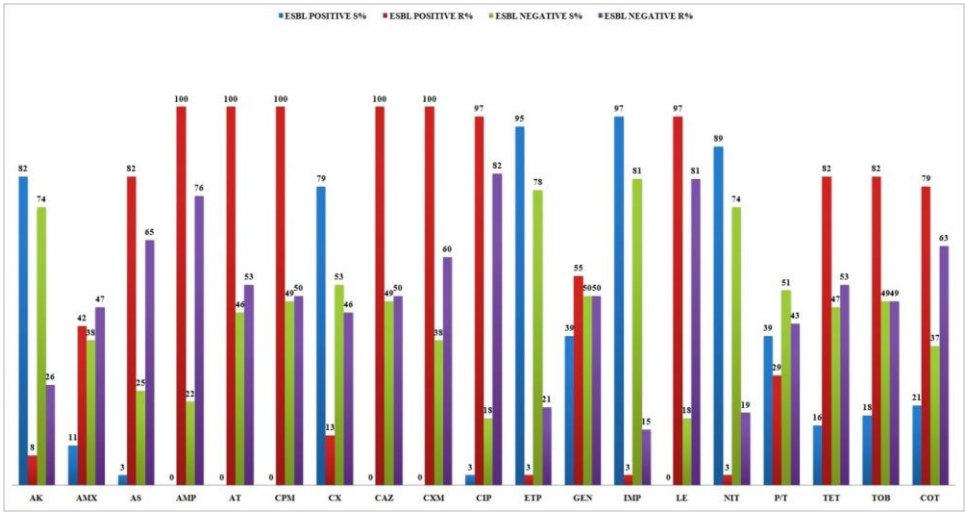

Fig.1 Antibiogram showing Sensitivity and Resistance Patterns of *E. coli* in hospitalized patients
S%= Sensitivity; R% = Resistant

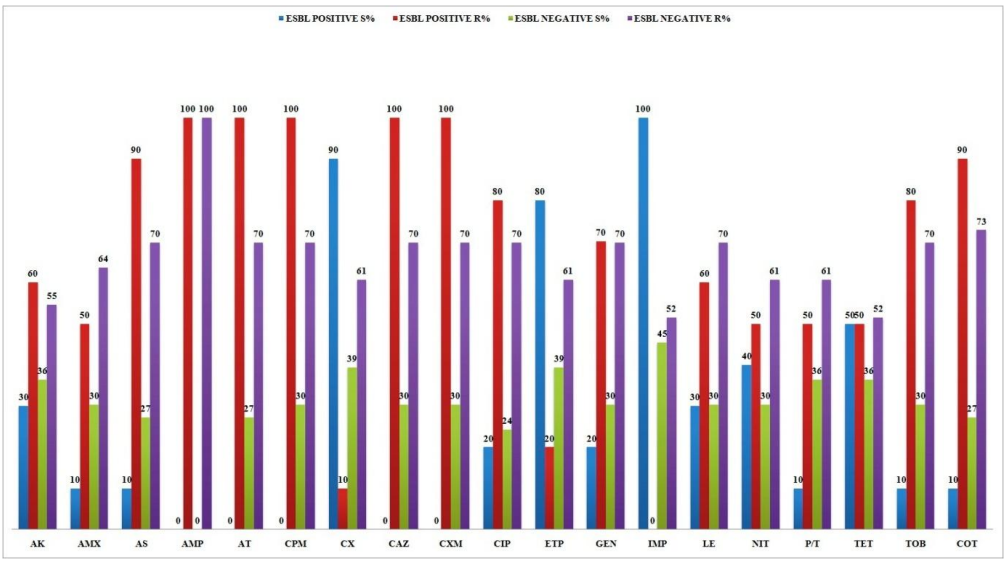

Fig.2 Antibiogram showing Sensitivity and Resistance Patterns of *K. pneumoniae* in hospitalized patients S%= Sensitivity; R% = Resistant

The present study evaluated the antibiogram of the ESBL producing and non-producing strains isolated from the hospitalized patients from in and around Gurugram, Haryana. To the best of our knowledge, this is the first research from our area with an exclusive focus on investigating the current prevalence and antibiogram among ESBL producing *E. coli* and *K. pneumoniae* the predominant uropathogens, globally.

Urinary tract infection is known as the one of the most common infection in patients with hospitalization[1]. The spread of drug resistance among gram-negative bacteria leads to the appearance of strains resistant to the antibiotics. These strains cause the development of UTIs resistant to the antibiotic therapy[12].

The positive culture rate with significant colony counts found among hospitalized patients was 33.11%. In the other study done at Jaipur showed 41.8%[13] which was higher than our study and similar higher results were seen in various other studies[14–16]. The antibiotic sensitivity pattern has changed over time and in different areas, but the spectrum of agents causing Urinary tract infection has remained comparatively invariable, with *E. coli* being the most common isolate[17]. In the current study, females were found to be more infected with the urinary tract infection as compared to males (Females:47.27 %; Males:20.26%, p-value: 0.000). The findings were contradictory to the study done by Bajpai *et al.*, and Singhal *et al.*, which found male were more prevalent in UTI as compared to females [13,18]. These findings were in line with the other studies done by different authors in different regions[10,19,20].

In the present study, *E. coli* was the most common isolate (44.73%). This was similar to the studies conducted by other researchers[16,21,22]. However, studies from some other parts of the country had shown higher frequency rates (65-90%)[23–25]. This variation might be due to the different environmental conditions in different areas. Prevalence of *K. pneumoniae* in hospitalized patients was 18.14% which was higher than the study conducted by Singhal *et al.* (11.0%)[13].

Prevalence of total ESBL production among all analysed uropathogens in the current study was 20.25% whereas lesser than the study conducted by Khurana *et al.* (26.6%) and

Tankhiwale *et al.* (48.3%)[26,27]. In the present study reported 35.85% *E. coli* ESBL positive isolates resembles the study published by Kumar *et al.* (39.0%)[28] and unlike those reported by Singhal *et al.* (62.0%), Maya *et al.* (75.5%) and Ramesh *et al.* (60.7%)[13,29,30]. 23.26% of the *K. pneumoniae* strains were found to be ESBL producer which is closer to the study done in Algeria (20.0%)[31]. In Pakistan, the prevalence was 36%[32]. In India, 68% were ESBL producing[33]. Studies have also shown an increase in ESBL- producing strains of *K. pneumoniae*, 29% in Spain[34], 28.4% in Taiwan[35] and 44% in the USA[36]. In light of the above findings, it is clear that the prevalence of a wide variety of ESBL enzymes is rising. It seems that increased and prolonged duration of hospitalization and treatment procedures, as well as frequent use of urinary catheters in hospitals, are responsible for the emergence of resistant strains and transfer of resistant genes to other bacteria.

Our study confirms the Global trend towards the increased resistance to the β-lactam group of antibiotics. ESBL producing bacteria may not be detectable by routine disc diffusion sensitivity testing, leading to the inappropriate use of antibiotics and failure in the treatment. It was emphasized that Institutions should employ appropriate tests for their detection and avoid indiscriminate use of third-generation cephalosporins. The treatment should only be given after the culture and sensitivity test report to prevent the MDR.

Antibiotic resistance showed by different isolates is one of the barricades that might hinder a successful treatment. Widespread use of antibiotics exerts the selective pressure that acts as a driving force in the development of the resistance to various antibiotics[18]. The detailed insight of the antibiogram is illustrated in Figure 1 and 2. Constant survey of the antibiotic-resistant pattern plays a very crucial role in the empiric treatment of UTIs.

In the present study, all ESBL positive *E. coli* and *K. pneumoniae* were found to be MDR due to which the treatment options remained very limited in the hospital settings. In comparison with other studies done, A very high MDR rates of 91.66% and 87.5% among ESBL positive *E. coli* and *K. pneumoniae* were obtained in this study[37]. A comparable MDR rate of 83% among *E. coli* isolates was reported in a study done in Peshawar, Pakistan[38].

In the study, 97% sensitive to ESBL positive isolates and 100% in ESBL positive *K. pneumoniae* isolates. Hence carbapenems can be the alternative treatment to the third-generation cephalosporins, fluoroquinolones and MDR strains (≥ 3antimicrobial classes) in the hospitalized patients due to ESBL positive uropathogens. In comparison to the study conducted by Aggarwal *et al.* 100% Imipenem sensitivity was observed[4]. Similar kind of findings were observed in the study conducted by different authors[39–42].

In earlier studies, prolonged hospitalization, Foley's catheterization, prior surgery, and ICU stay were found to be risk factors[43–45]. Good infection control practices and antibiotic management interventions are instrumental in preventing the emergence of outbreaks due to ESBL producing isolates, especially in high-risk areas such as the medical ICU, the neonatal ICU, and oncology units. Educational programs for medical, nursing and another supporting hospital to increase awareness of ESBLs should also be developed.

This study revealed the resistant rates of 70.0% and 60% to the aminoglycosides, Gentamicin and Amikacin by ESBL positive *K. pneumoniae* isolates. In comparison, *E. coli* shown a much low resistance rate: Gentamicin 55.0 %; Amikacin: 8.0%. In contrast, *K. pneumoniae* showed resistance to Gentamicin (69%) and Amikacin (38%) while 59% and

33% resistance rates were confirmed by *E. coli* isolates in a study done in Indore, India[46]. A resistance rate of 46.7% to gentamicin was demonstrated by *K. pneumoniae* isolates in a report from Karachi, Pakistan[47], which is similar to results in this study. This release supports that aminoglycosides have excellent activity against clinically significant gram-negative bacilli[48]. The resistance rates of ESBL positive *E. coli* and *K. pneumoniae* to nitrofurantoin were 3.0% and 50.0%, respectively. Resistance rate (12%) by *E. coli* isolates was shown in a report from Indore, India[46].

In conclusion, *E. coli* and *K. pneumoniae* were the most predominant uropathogens and ESBL positive due to which MDR has been increased. MDR to commonly used antimicrobials in uropathogens has caused considerable alarm which suggests the importance of judicious use of antimicrobials. Carbapenems were the most promising drugs against Gram-negative bacilli. Nitrofurantoin can be considered as the alternative option in the empirical treatment of UTI. It is suggested to not to start any antibiotics without the culture and sensitivity report.

In the present study, the global trend toward increased resistance to β-lactam antibiotics was confirmed. It was emphasized that institutions with a high prevalence of third-generation cephalosporin resistant organisms should employ appropriate tests for their detection and avoid indiscriminate use of third-generation cephalosporins. Also, the incidence and antibiogram of ESBL producers differ geographically. Hence, such institutional studies will help in the formulation of antibiotic policy for a particular geographical area.

The strict antibiotic policy should be adopted in hospitals to estimate the impact of higher resistance in bacteria and to take steps for reducing the resistance. There are several possible methods for overcoming resistance including reduced use of antibiotics, use of synergistic combinations, the addition of an anti-resistance factor, attacking the underlying disease, improving the hygienic measures and regular surveillance studies.

This report documents the emergence and occurrence of ESBL producing *E. coli* and *K. pneumoniae* in urinary isolates in our area. A high prevalence of ESBL producing *E. coli* and *K. pneumoniae* was observed and confirmed in the urinary isolates. A strict hospital infection control policies and prudent antimicrobials use regimens to be adopted by the physicians. It is essential and mandatory to have regular and routine monitoring of ESBL producing clinical isolates in clinical laboratories.

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