

Prevalence of β -lactamase production and multi-drug resistance among uropathogenic *Escherichia coli* isolates at a tertiary care hospital of North-western India



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ABSTRACT

Background: *E. coli* is the most common organism causing UTI. Inappropriate and widespread use of broad-spectrum antibiotics has resulted in development of multi-drug resistance and β -lactamases producing strains. **Aims and Objective:** To assess β -lactamase production and multi-drug resistance among uropathogenic *E. coli* isolates. **Materials and Methods:** A total of 145 *E. coli* urinary isolates were included in this study. The isolated organisms were identified by conventional microbiological procedures. Antimicrobial susceptibility was performed by Kirby Bauer disk diffusion method. Isolates were screened for extended spectrum β -lactamase production and confirmed by phenotypic confirmatory double disc synergy test. Isolates resistant to ceftiofuran were considered potential AmpC producers confirmed by AmpC disc test and modified three dimensional test. Isolates resistant to imipenem and meropenem were considered potential carbapenemase producers and confirmed by mCIM test. **Results:** Out of 145 isolates 91 (62.76%) were isolated from males and 54 (37.24%) from females. Majority of the isolates were obtained from the age group of 21-30 years (48.96%) followed by 31-40 years (14.48%). Highest susceptibility was seen towards fosfomycin (94.48%), tigecycline (87.59%), nitrofurantoin (77.24%). Highest resistance of 81.38% was observed against ampicillin while more than 70.0% resistance observed with cefazolin, cefotaxime, ciprofloxacin, levofloxacin and amoxiclav. Multi-drug resistance was observed in 85.51% isolates and 4.14% were found to be possible XDR. Among these isolates frequency of β -lactamase production was ESBL (45.51%), AmpC (28.96%) and carbapenemase (28.96%). **Conclusion:** Drug resistance due to β -lactamases production is emerging as a serious threat in UTI; routine screening of these β -lactamases will prevent treatment failures.

Key words: β -lactamases; *E. coli*; Multi-drug resistant; Urinary tract infection

INTRODUCTION

Urinary tract infection (UTI) is a term that describes any infection involving any part of the urinary tract, namely the kidneys, ureters, bladder and urethra. UTI can be asymptomatic (subclinical infection) or symptomatic (disease).¹ Bacteria are the prime agents responsible for causing the infections among humans but the role of certain fungi and viruses cannot be overlooked. UTIs are caused by both Gram-negative and Gram-positive bacteria. *E. coli* is most common organism causing UTI which accounts

for up to 90% of cases followed by *Klebsiella* spp., *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. Among gram positive bacteria, *Enterococcus* spp. is the most common organism responsible for UTI followed by *Staphylococcus aureus* and Coagulase negative Staphylococci especially *Staphylococcus saprophyticus* in sexually active females.²

Inappropriate and widespread use of antibiotics has led to the emergence of drug resistance mechanisms like the production of extended spectrum β -lactamases (ESBL), Amp C β -lactamases and carbapenemases.³

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ESBL are type of β -lactamases that causes bacterial resistance to the penicillins, first, second and third generation cephalosporins and aztreonam by causing hydrolysis of these antibiotics and which are inhibited by β -lactamase inhibitors such as clavulanic acid.⁴ AmpC are a kind of β -lactamases that are active on cephalosporins and can also hydrolyze cephamycins (cefoxitin and cefotetan); oxyiminocephalosporins such as ceftazidime, cefotaxime and ceftriaxone and monobactams such as aztreonam. Inhibitors such as clavulanic acid, sulbactam and tazobactam have much less effect on AmpC β lactamases.⁵ Carbapenem is the drug of choice to treat the infections caused by ESBL producing bacteria. However, in recent decades the emergence of carbapenemase producers that are resistant to the carbapenems are creating global issue in infection control.

The aim of this study was to identify the current prevalence of β -lactamase producing uropathogenic *E.coli* and multi-drug resistance among them in our hospital.

MATERIALS AND METHODS

This prospective study was conducted in department of microbiology from June to December 2019. Midstream urine samples were collected from symptomatic patients from both inpatient and outpatient departments. Samples were collected and transferred according to recommended guidelines to prevent contamination.

The urine samples were inoculated on MacConkey's agar and blood agar plates using calibrated loop and incubated aerobically at 37°C for 24 hours. Single type of colonies $>10^5$ per ml of urine was considered significant. Significant isolates were biochemically characterized by using indole production, citrate utilization, urease production, triple sugar iron agar and motility.⁶ Samples from which significant growth of *E.coli* was identified were included in the study.

Antibiotic susceptibility was tested by Kirby Bauer disc diffusion method against a panel of antibiotics using bacterial suspension matched to 0.5 McFarland standards as inoculum on Mueller Hinton agar (MHA) (HiMedia Laboratories Pvt. Limited, India). The antibiotics used were Amikacin (30 μ g), Gentamicin (10 μ g), Cefoperazone-sulbactam (75+30 μ g), Imipenem (10 μ g), Meropenem (10 μ g), Cefazolin (30 μ g), Cefotaxime (30 μ g), Cefepime (30 μ g), Cefoxitin(30 μ g),Ciprofloxacin(5 μ g),Levofloxacin (10 μ g), Trimethoprim+sulphamethoxazole (1.25+23.7 μ g), Piperacillin+tazobactam (100 μ g+10 μ g), Tigecycline (15 μ g), Ampicillin (10 μ g), Amoxicillin+clavulanic acid (20 μ g+10 μ g), Fosfomycin (200 μ g+50 μ g glucose-6-phosphate), Nitrofurantoin (300 μ g), Tetracycline (30 μ g) (HiMedia Laboratories Pvt. Limited, India). The zones of

inhibition were interpreted according to CLSI guidelines 2019.⁷ *E. coli* ATCC 25922 was used as control strain. Isolates non-susceptible ≥ 1 agent in ≥ 3 antimicrobial categories were considered as multi-drug resistant (MDR); non-susceptible to ≥ 1 agent in all but ≤ 2 antimicrobial categories as extensively drug resistant (XDR) and non-susceptible to ≥ 1 agent in all antimicrobial categories as pan-drug resistant (PDR).⁸

Screening for ESBL production of *E.coli* was done by the disc diffusion method. The isolates producing a zone diameter ≤ 27 mm against cefotaxime (30 μ g) or zone diameter ≤ 22 mm against ceftazidime (30 μ g) were considered as presumptive ESBL producers. These isolates were confirmed by phenotypic confirmatory double disc synergy test (PCDDT).⁷ Isolates showing resistance to cefoxitin (inhibition zone ≤ 18 mm) by disc diffusion method were considered potential AmpC producers and further tested by AmpC disc test and modified three dimensional test.⁹ Isolates showing resistance to imipenem & meropenem (inhibition zone ≤ 19 mm) by disc diffusion method were considered potential carbapenemase producers and further tested by mCIM test (modified carbapenem inactivation method).⁷ Ethical clearance was obtained from ethical approval committee of the institute.

Statistical analysis

Statistical analysis was done using computer software statistical package for the social sciences (SPSS) version 20.0. The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analyzed by using chi square test. Significance level for tests was determined as 95% ($P < 0.05$).

RESULTS

A total of 145 isolates of *E.coli* were included in the study. Among these isolates 91(62.76%) were from male patients and 54(37.24%) were from female patients. The age group most commonly affected was 21-30 years (48.96%) followed by 31-40 years (14.48%). Among male patients most of the isolates were obtained from indoor patients (33.10%) and among female patients from outdoor patients (22.06%) (Table 1).

Ninety seven isolates were screened positive for ESBL production, 66 isolates (68.04%) were confirmed as positive by phenotypic confirmatory disc diffusion test (PCDDT). Screening test for Amp C production was positive in 85 isolates, 42 (49.41%) isolates were confirmed by Amp C disc test and modified three dimensional tests. Out of 96 isolates screened positive for carbapenemase production, 42 (43.75%) were confirmed by mCIM test.

Antibiotic resistance was seen higher among β -lactamase producers than non β -lactamase producers. The difference in resistance between β -lactamase producers and non β -lactamase producers was not significant with cefepime, piperacillin-tazobactam, tigecycline and fosfomycin (Table 2).

The difference in antibiotic resistance pattern among ESBL, AmpC and carbapenemase producing isolates was statistically not significant (Table 3).

Out of 145 isolates 124 isolates (85.51%) were found to be multi-drug resistant and 6 isolates (4.14%) were found to be possible XDR (Table 2). None of the isolates were pan-drug resistant. Multi-drug resistance was observed among all isolates of β -lactamase producers and 70.0% among non β -lactamase producers. Among MDR isolates ESBL, Amp C, carbapenemase production was seen in 49.19%, 30.64%, 32.26% isolates respectively. Coproduction of two β -lactamases was seen in 48.37% isolates and all 3 β -lactamases were produced together in 7.26% isolates.

Table 1: Distribution of *E. coli* isolates in IPD and OPD as per Age Groups and Sex

Age Groups in Yrs	Male			Female			Total		
	IPD	OPD	Total N (%)	IPD	OPD	Total N (%)	IPD	OPD	Total N (%)
< 10	0	4	4 (2.76)	1	2	3 (2.07)	1	6	7 (4.83)
11-20	2	5	7 (4.83)	0	4	4 (2.76)	2	9	11 (7.59)
21 – 30	20	17	37 (25.52)	14	20	34 (23.45)	34	37	71 (48.96)
31-40	10	5	15 (10.34)	3	3	6 (4.14)	13	8	21 (14.48)
41-50	11	7	18 (12.41)	1	2	3 (2.07)	12	9	21 (14.48)
51-60	2	2	4 (2.76)	1	0	1 (0.69)	3	2	5 (3.45)
61-70	2	1	3 (2.07)	1	1	2 (1.38)	3	2	5 (3.45)
>70	1	2	3 (2.07)	1	0	1 (0.68)	2	2	4 (2.76)
Total	48	43	91 (62.76)	22	32	54 (37.24)	70	75	145 (100.00)

Level of significance: at 7 DF, *= 0.05 level of significance=14.67, Age and IPD/OPD wise: χ^2 : 8.129; NS $P>0.05$, Age and Gender –wise: χ^2 : 9.113; NS $P>0.05$, IPD/OPD and Gender –wise: χ^2 : 2.329; NS $P>0.05$

Table 2: Antibiotic Resistance Pattern of β -lactamase Producing *E. coli* isolates

Antibiotic	Resistance (145) N (%)	β -Lactamase producers (95) N (%)	Non β -Lactamase producers (50) N (%)	Z value	P value
Amikacin	49 (33.79)	41 (43.15)	8 (16.00)	3.37**	<0.01
Gentamycin	80 (55.17)	63 (66.31)	17 (34.00)	3.66**	<0.01
Cefoperazone-sulbactam	74 (51.03)	60 (63.15)	14 (28.00)	4.00**	<0.01
Imipenem	96 (66.20)	83 (87.36)	13 (26.0)	7.02**	<0.01
Cefazolin	107 (73.79)	87 (91.57)	20 (40.0)	6.16**	<0.01
Cefoxitin	85 (58.62)	77 (81.05)	8 (16.0)	7.38**	<0.01
Cefotaxime	115 (79.31)	85 (89.47)	30 (60.0)	3.85**	<0.01
Cefepime	101 (69.65)	67 (78.82)	34 (68.0)	1.39 ^{NS}	>0.05
Ceftazidime	97 (66.90)	88 (92.63)	9 (18.0)	8.51**	<0.01
Ciprofloxacin	110 (75.86)	87 (91.57)	23 (46.00)	5.58**	<0.01
Levofloxacin	110 (75.86)	85 (89.47)	25 (50.00)	4.87**	<0.01
Cotrimoxazole	90 (62.06)	72 (75.78)	18 (36.00)	4.54**	<0.01
Piperacillin-Tazobactam	48 (33.10)	31 (32.63)	17 (34.00)	0.16 ^{NS}	>0.05
Tigecycline	18 (12.41)	14 (14.73)	4 (8.00)	1.20 ^{NS}	>0.05
Ampicillin	118 (81.37)	86 (90.52)	32 (64.00)	3.59**	<0.01
Amoxiclav	110 (75.86)	87 (91.57)	23 (46.00)	5.58**	<0.01
Fosfomycin	8 (5.52)	7 (7.37)	1 (2.0)	1.44 ^{NS}	>0.05
Nitrofurantoin	33 (22.76)	27 (28.42)	6 (12.0)	2.32*	<0.05
Tetracycline	92 (63.45)	73 (76.84)	19 (38.0)	4.45**	<0.01
Multi-drug resistant (MDR)	124 (85.51)	89 (93.68)	35 (70.0)	-	-
Possible XDR	6 (4.14)	6 (6.31)	0	-	-

NS=Not Significant, *= Significant at 0.05 level of significance, **= Significant at 0.01 level of significance, *0.05 level of significance=1.96 and ** 0.01 level of significance=2.58

Table 3: Antibiotic resistance pattern of ESBL, AmpC and carbapenemase producing *E. coli* isolates

Antibiotics	ESBL producers N(%)	Amp C producers N(%)	Carbapenemase producers N(%)	Z value	P value
Amikacin	28 (42.42)	21 (50.00)	15 (35.71)	1.76 ^{NS}	>0.05
Gentamycin	44 (66.66)	32 (74.41)	27 (64.28)	1.60 ^{NS}	>0.05
Cefoperazone-sulbactam	42 (63.63)	31 (72.09)	26 (61.90)	1.62 ^{NS}	>0.05
Imipenem	54 (81.81)	38 (88.37)	42 (100.00)	8.98 ^{**}	<0.01
Cefazolin	62 (93.93)	41 (95.34)	37 (88.09)	3.13 ^{NS}	>0.05
Cefoxitin	54 (81.81)	42 (100.00)	32 (76.19)	10.68 ^{**}	<0.01
Cefotaxime	58 (87.87)	39 (92.85)	38 (90.47)	0.72 ^{NS}	>0.05
Cefepime	46 (69.69)	30 (71.42)	25 (59.52)	1.65 ^{NS}	>0.05
Ceftazidime	66 (100.00)	40 (95.23)	36 (85.71)	10.41 ^{**}	<0.01
Ciprofloxacin	57 (86.36)	38 (90.47)	41 (97.61)	3.84 ^{NS}	>0.05
Levofloxacin	58 (87.87)	37 (88.09)	40 (95.23)	1.78 ^{NS}	>0.05
Cotrimoxazole	52 (78.78)	33 (76.74)	30 (71.42)	0.90 ^{NS}	>0.05
Piperacillin-Tazobactam	41 (62.12)	28 (65.11)	27 (64.28)	0.23 ^{NS}	>0.05
Tigecycline	11 (16.66)	8 (19.04)	6 (14.28)	0.34 ^{NS}	>0.05
Ampicillin	58 (87.87)	38 (90.47)	39 (92.85)	0.72 ^{NS}	>0.05
Amoxiclav	58 (87.87)	39 (92.85)	34 (80.95)	2.72 ^{NS}	>0.05
Fosfomycin	4 (6.06)	5 (11.63)	0 (0.00)	5.27 ^{NS}	>0.05
Nitrofurantoin	20 (30.30)	12 (28.57)	12 (28.57)	0.05 ^{NS}	>0.05
Tetracycline	49 (74.24)	36 (85.71)	33 (78.57)	2.01 ^{NS}	>0.05

NS=Not Significant, *= Significant at 0.05 level of significance, **= Significant at 0.01 level of significance, 0.05 level of significance=5.991 and 0.01 level of significance=9.210

DISCUSSION

Urinary tract infections represent one of the most common diseases encountered in the routine clinical practice, with an estimated 150 million UTIs per annum worldwide. The predominant uropathogens for UTIs are gram negative bacteria with *E.coli* accounting for the highest prevalence in most instances.¹⁰ In our study there was male preponderance of 62.76% for this infection while in females it was 37.24%. This male preponderance could be due to the fact that the samples were received from departments other than obstetrics and gynaecology. Age group analysis revealed that significant numbers of *E.coli* were isolated from age group of 21-40 years (63.44%) in both males (35.86%) and female patients (27.59%), similar observation was seen in studies by Bakshi R et al. (77.35%),¹¹ Rahman MS et al. (56.0%),² Shakya P et al. (42.19%),¹² Sahu RK et al (40.85%)¹³ and Das B et al (58.84%).¹⁴

Increasing rates of β -lactamase producing bacteria are causing serious UTI in the society and hospitals world-wide. In our study ESBL production was observed in 45.51% of *E.coli* isolates which is in concordance with findings in many studies from different parts of India.^{3,11,15,19} In the current study, the Amp C production was seen in 28.96% (42/145) isolates, similar finding has been reported by Bora A et al.²⁰ from Assam. Compared to these findings other studies have reported a lower prevalence of the AmpC producers.^{1, 11, 16, 17, 19, 21, 22} while Shreshtha UT et al.²³ reported a higher prevalence of 46.3%. Prevalence of coproduction of AmpC among ESBL isolates in the present study was 42.86%, which is higher than Gupta V et al.8.0%,¹⁶ Mwinga MM et al. 10.77%²⁴ and Shreshtha UT et al.19.4%.²³

Prevalence of carbapenemase producing *E.coli* isolates in the present study was 28.96%. Varied prevalence was observed in other studies; Shreshtha UT et al. (11.2%),²³ Mwinga MM et al (18.4%).²⁴ No significant difference was seen between β -lactamases producing isolates from out-patients and in-patients (P=> 0.05).

Significant difference in antibiotic resistance pattern was found between β -lactamase and non β -lactamase producers in our study. Among β -lactamase producers fosfomycin resistance was lowest (7.37%). Low resistance to fosfomycin has also been observed by Das B et al. (7.7%)¹⁴ and Rahman MS et al. (4.0%).² In few studies all the β -lactamase producing isolates were found to be susceptible to fosfomycin.^{11,16} Resistance to nitrofurantoin in most studies was in the range of 10-20%.^{11,14,18,19} In our study and Ranjini CY et al.³ nitrofurantoin resistance was seen in 28.42% and 26.77% isolates respectively while Gupta V et al.¹⁶ found no resistance. The ICMR, antimicrobial resistance surveillance network, 2018 data has reported 88.1% and 86.0% of the isolates to be sensitive to two old antibiotics, fosfomycin and nitrofurantoin respectively.²⁵ In most of the studies no resistance to imipenem was observed^{14,16,19} but we have observed a high resistance of 66.21%. Chauhan S et al.¹⁹ and Das B et al.¹⁴ found no resistance to tigecycline while in this study 14.73 % isolates were resistant. Varied range of resistance to amikacin was reported: 6.0% to 55.0%.^{3,11,16,18,19} Moderate resistance to piperacillin-tazobactam was found in the present study (32.63%) and Chauhan S et al.¹⁷ reported 46.0%, however most authors found a low resistance of 5-16%.^{2,11,14,16} Resistance to co-trimoxazole, ampicillin and fluoroquinolones was high in most of the studies.

Among non β -lactamase producing isolates fosfomycin was least resistant (2.0%) followed by tigecycline (8.0%), nitrofurantoin (12.0%), amikacin and ceftoxitin (16.0%), ceftazidime (18.0%).

In this study we have observed good susceptibility with fosfomycin, tigecycline and nitrofurantoin among both β -lactamase and non β -lactamase producing isolates. Resistance to cefepime, piperacillin-tazobactam, tigecycline and fosfomycin among β -lactamase and non β -lactamase producing isolates was statistically insignificant. All β -lactamase producing isolates were found to be MDR in the present and in other studies.^{3,11,14,16}

CONCLUSION

In the majority of UTI cases, antibiotics are given empirically before bacteriology culture results are available. The β -lactam antibiotics are among the most frequently prescribed antibiotics world-wide, the selective pressures created by the indiscriminate use of the β -lactam antibiotics have led to the selection of a variety of mutant forms of β -lactamases such as the ESBL, AmpC and carbapenemase. The genes for β -lactamases are usually found on R-plasmids encoding resistance to aminoglycosides, sulfonamides, tetracyclines and other antibiotics. Therefore, the infections caused by β -lactamases producing bacteria pose serious treatment challenges. Information on prevailing levels of antimicrobial resistance in this study would help clinicians to be aware of the reasons of treatment failures caused by serious infections due to these bacteria and guide for appropriate empirical antimicrobial therapy.

To combat the prevalence of antimicrobial resistance, strict antibiotic policies to limit the indiscriminate use of cephalosporins and carbapenems in the hospital and effective infection control measures like hand washing and barrier precautions should be implemented.

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