DOI: 10.7860/JCDR/2013/4990.2796

Original Article

Microbiology Section

Multidrug-Resistance and Extended Spectrum Beta-Lactamase Production in Uropathogenic *E. Coli* which were Isolated from Hospitalized Patients in Kolkata, India

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ABSTRACT

Background and Objective: Urinary Tract Infections (UTIs) are mostly caused by *Escherichia coli*. The appropriate therapy demands a current knowledge on the antimicrobial susceptibility pattern amongst these pathogens, as an inappropriate use of antibiotics may lead to complications and treatment failure. The UTIs which are caused by multidrug resistant Extended-Spectrum Beta-Lactamase (ESBL) producing bacteria further pose a severe problem, as the treatment options are limited. The aim of this study was to identify the pattern of multi drug resistance amongst the uropathogenic *E. coli* (UPEC) isolates which were obtained from hospitalized patients.

Materials and Methods: Forty UPEC were isolated from 200 urine samples of hospitalized patients who were clinically suspected for UTIs. Antimicrobial susceptibility screening was performed by using 16 antibiotics, by the Kirby Bauer disk diffusion technique. The isolates which were resistant to the third generation cephalosporins were subjected to the ESBL confirmatory test by using drug and drug-inhibitor combination disks by following the CLSI guidelines.

Results: All the 40 isolates except three were multidrug resistant. They showed the highest sensitivities for nitrofurantoin (72.5%) and amikacin (70%). A high level of resistance was observed against ampicillin (97.5%), nalidixic acid and cefelexin (95%), amoxicillin (92.5%), cotrimoxazole (82.5%) and ciprofloxacin (80%) respectively. Thirty different antibiotic resistance patterns were observed against the different antibiotics. Twenty-eight out of the 40 isolates were resistant to the third generation cephalosporins. However, the phenotypic test for the ESBL confirmation indicated that eighteen out of the twenty-eight isolates were ESBL producers and that eleven different drug resistance patterns were observed amongst them.

Conclusions: Therefore, this study accounts for the varied multidrug resistance pattern amongst the uropathogenic *E. coli* which were isolated from hospitalized patients in Kolkata, an eastern region of India. Nitrofurantoin and amikacin should be assigned as potent drugs to treat this infection in this region of the country. These varied resistance patterns present major therapeutic and infection control challenges and they suggest a heterogeneous population of the uropathogenic *E. coli* isolates which circulate in this sector of India.

Key Words: Antibiotic susceptibility, Urinary tract infection, Uropathogenic *E. coli*, Extended- spectrum beta lactamase

INTRODUCTION

Urinary Tract Infections (UTIs) represent one of the most common diseases which are encountered in the medical practice today, with an estimated 150 million UTIs per annum worldwide. *Escherichia coli* was the most frequently found bacteria in both the community acquired and the hospitalized UTI patients [1]. The introduction of the antimicrobial therapy has contributed significantly to the management of this infection. However, the resistance to the anti-biotic treatment in the patients with UTIs was a representative example of the increasing problem of the antimicrobial resistance [2]. The Extended Spectrum Beta Lactamases (ESBLs) that hydrolyse the oxyimino beta lactams like ceftazidime, cefotaxime, ceftriaxone and monobactum but have no effect on the cephamycins, carbapenem and related compounds have emerged as an important mechanism of resistance amongst these uropathogens. They were first detected in western Europe in the mid-1980s. Since then, their incidence has been increasing steadily. A large number of outbreaks of the infections which are caused by ESBL producing organisms have been described in every continent of the globe [3]. Unfortunately, the ESBL-producing organisms often also have resistance determinants to other important antibiotic groups such as the aminoglycosides and the fluoroquinolones, leaving an extremely limited range of effective agents [2]. A delay in giving the appropriate therapy for the infections which are caused by the ESBL producing bacteria can cause severe complications.

It is important to realize that there may be marked differences in the antibiotic resistance pattern between various geographic areas within a vast country like India. Since most of the UTIs are treated empirically, the selection of the antimicrobial agent should be determined, not only on the basis of the most likely pathogen, but also on the basis of its expected susceptibility pattern. Thus, the knowledge of the local antimicrobial susceptibility patterns of the common uropathogens is essential for providing a prudent empiric therapy. Therefore, with the reports on the high prevalence of multidrug resistance and ESBL production amongst the uropathogenic *E. coli* from different regions of India [3,4] and the paucity of information on their antibiotic susceptibility, especially of the uropathogens from Kolkata, an eastern region in India, the

present study was undertaken to characterize the uropathogenic *E. coli* isolates which were circulating in this region with respect to the susceptibility to the antimicrobial agents and to identify the possible resistance trends. The prevalence of the potential ESBL producers was also explored.

MATERIALS AND METHODS

Sample Collection and Bacteriology

A total of 200 urine samples were collected from hospitalized patients who were clinically suspected for UTIs. Among these, 110 urine samples yielded significant growth. A significant monomicrobic bacteriuria was defined as the culture of a single bacterial species from the urine sample at a concentration of $>10^5$ cfus/ml. Only a single positive culture per patient was included in the analysis. *E. coli* were detected in 40 isolates out of 110 by standard biochemical tests [5]. The media which were used in the study included, MacConkey's Agar, Eosin Methylene Blue Agar and Luria Bertani Broth (Hi-Media, Mumbai).The cultures were incubated at 37ºC for 24 hrs respectively. These *E. coli* isolates were subcultured on Luria Bertani broth and they were maintained on Luria bertani agar plates at 4ºC for further studies. The study protocol was approved by the institutional ethical committee.

Antibiotic Susceptibility Testing

The susceptibilities of the isolates to different antibiotics were tested by the Kirby Bauer disk diffusion method by using Muller Hinton Agar against selected antibiotics, namely ampicillin (AMP;10 µg), amoxicillin (AMX;10µg), amikacin (AK; 10µg), gentamicin (GEN; 10µg), tobramycin (TOB; 10 µg), cefelexin (CN; 30 µg), ceftriaxone (CTR; 30 µg), ceftazidime (CAZ;30 µg), cefotaxime (CTX; 30 µg), nalidixic acid (NA; 30 µg), ciprofloxacin (CIP; 5 µg), levofloxacin (LE; 5µg), lomefloxacin (LOM; 5 µg), ofloxacin (OF;5 µg), cotrimoxazole (COT; 25 µg) and nitrofurantoin (NF; 300 µg),(Hi-Media, Mumbai). The sensitivity test was standardized by using an *E. coli* (ATCC 25922) strain. The inhibition zone size was interpreted by using the standard recommendation of the Clinical Laboratory Standard Institute [6]. An isolate was considered as multidrug resistant if it was resistant to ≥3 groups of antibiotics.

The ESBL Confirmatory Test

All the *E. coli* isolates which were collected from the urine of hospitalized patients, which were resistant to at least CAZ, CTR and/or CTX were subjected to the ESBL confirmatory test by using the CAZ and Ceftazidime-Clavulanic Acid (CAC) and the CTX and Cefotaxime-Clavulanic Acid (CEC) combination disks. A difference of 5 mm between the zone of inhibition of a single disk and in combination with clavulanic acid (inhibitor) was confirmed to be produced by an ESBL positive isolate [6].

Statistical Analysis

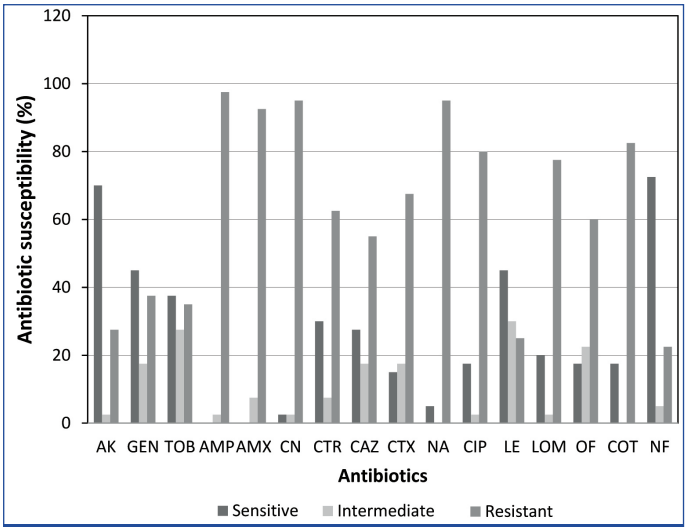
To analyze the data, it was reported in the form of the diameter of the inhibition zone during the susceptibility testing of all the bacterial isolates by the disc diffusion test against different classes of antimicrobial agents. One-way ANOVA was performed to check the significant difference among the different groups. A difference was considered to be significant if the probability that chance would explain the results, was reduced to less than 5% ($p \leq 0.05$).

RESULTS

A total of 200 urine samples was considered for the urine culture. Significant bacteriuria was observed in 110 (55%) isolates. Moreover, amongst the 110 isolates, *E. coli* was detected in 40 (36%) isolates. The resistance patterns of these *E. coli* isolates against a spectrum of 16 selected antimicrobial agents of different classes were analyzed [Table/Fig-1]. The isolates showed the highest sensitivity against NF (72.5%) and AK (70%), followed by GEN (45%), LE (45%) and TOB (37.5%). However, the incidence of an intermediate resistance against LE (30%), TOB (27.5%) and OF (22.5%) was also observed. Amongst the third generation cephalosporins which were tested, it was found that the isolates were mostly resistant to CTX (67.5%) than CTR (62.5%) and CAZ (55%) respectively. Moreover, the intermediate resistance against CAZ (17.5%) was higher than that against CTR (7.5%) amongst the isolates which were analyzed. The highest resistance was observed against AMP (97.5%), NA (95%) and CN (95%), followed by that against AMX (92.5%), COT (82.5%) and CIP (80%) respectively. Furthermore, 26 CIP (65%) resistant isolates amongst the 40 were also resistant to the third generation cephalosporins. Therefore, the varied patterns of the antibiotic susceptibility among the 40 *E. coli* isolates against the 16 different antibiotics which were tested, has been summarized in [Table/Fig-2]. Almost all of the isolates except three which were included in this study, were found to be resistant to three or more groups of antibiotics which were tested and thirty different resistant patterns were observed amongst them [Table/Fig-3]. Each of these patterns was common in 1 or up to 3 isolates which were analyzed. Furthermore, One-way ANOVA analysis indicated that the difference in the antibiotic susceptibility pattern which was observed amongst the 40 isolates against the 16 different antibiotics which were tested was statistically significant ($p < 0.0001$). The ESBL phenotype confirmation test was performed on 28 isolates which were resistant to either all three third generation cephalosporins (CTR, CAZ, CTX) or any one, as was revealed by the disk diffusion technique. 18 out of the 28 cephalosporin resistant isolates were ESBL producers, as the zone of inhibition increased by >5mm when it was tested in the presence of a cephalosporin containing disk and the drug and drug inhibitor combination disks respectively. Moreover, the ESBL confirmatory test must always be performed with both the CTX-CEC and the CAZ-CAC combinations, as using either one combination may give

Antibiotics	E. coli isolates (n = 40)	
	Resistant (%)	Intermediate (%)
AMP	39(97.5)	1(2.5)
AMX	37(92.5)	3(7.5)
AK	11(27.5)	1(2.5)
GEN	15(37.5)	7(17.5)
TOB	14(35)	11(27.5)
CN	38(95)	1(2.5)
CTR	25(62.5)	3(7.5)
CAZ	22(55)	7(17.5)
CTX	27(67.5)	7(17.5)
NA	38(95)	0
CIP	32(80)	1(2.5)
LE	10(25)	12(30)
LOM	31(77.5)	1(2.5)
OF	24(60)	9(22.5)
COT	33(82.5)	0
NIF	9(22.5)	2(5)

[Table/Fig1]: Antimicrobial resistance amongst the uropathogenic *E. coli* isolated in this study



[Table/Fig-2]: Susceptibility of the uropathogenic *E. coli* isolates (n=40) to various antibiotics. AMP ; ampicillin (10 µg), AMX; amoxicillin (10µg), AK; amikacin (10µg), GEN; gentamicin (10µg), TOB; tobramycin (10 µg), CN; cefelexin (30 µg), CTR; ceftriaxone (30 µg), CAZ;ceftazidime (30 µg), CTX; cefotaxime (30 µg), NA; nalidixic acid (30 µg), CIP; ciprofloxacin (5 µg), LE; levofloxacin (5µg), LOM; Lomefloxacin (10 µg), OF;ofloxacin (5 µg), COT; cotrimoxazole (25 µg), NF; nitrofurantoin (300 µg). All assays were done in triplicate with each pathogenic isolate.

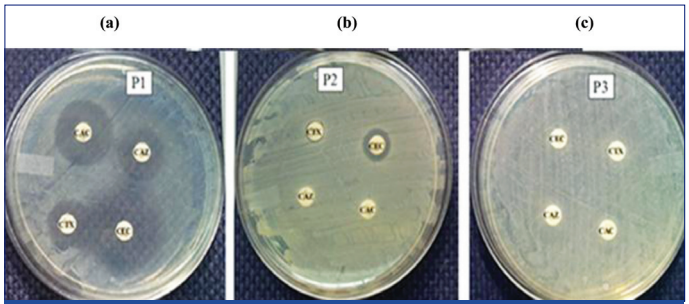
negative results [Table/Fig-4]. It was also observed that 17 out of the 18 ESBL producers were multidrug resistant [Table/Fig-5] and that eleven different antibiotic resistance patterns were observed amongst them. Each of these patterns was common in 1 or up to 3 isolates which were analyzed [Table/Fig-6].

DISCUSSION

A frequent irrational use of antibiotics changes the intestinal flora, leading to bacterial resistance [7]. In this study, we focused on the uropathogenic *E. coli* strains and their sensitivity patterns to different groups of antibiotics which were commonly administered to treat the infections. 37 out of the 40 isolates were multidrug resistant. An incidence of ESBL producers amongst the multidrug resistant *E. coli* strains was reported. A high incidence of Multidrug-Resistant (MDR) strains was also detected amongst the present isolates. About 92.5% were resistant to 3 or more of the tested antibiotics. The level of MDR amongst the UTI isolates was found to vary from country to country. For example, it was reported to be 7.1% in USA [8,9] while 42% of the UPEC isolates in Slovenia, in 2006, were MDR [10]. MDR causes major consequences such as the empirical therapy of the *E. coli* infections, as well as a possible co-selection of the antimicrobial resistance which is mediated by the MDR plasmids. In the present study, although the resistances to AMX (92.5%), COT (82.5%) and CIP (80%) were high, those against AMP (97.5%) NA (95%) and CN (95%) respectively were the highest. High levels of resistance to AMP, COT and NA had also been reported in other studies worldwide [10, 11]. The reports on the antibiotic susceptibility amongst the uropathogens which were isolated from different geographical locations in India revealed a high resistance against a majority of the antibiotics such as COT, AMX, GEN, CIP, CN and AK [12]. This resistance had been increasing considerably and it was primarily due to the excessive and the unnecessary use of antibiotics for non-therapeutic complaints. The WHO guidelines recommend COT and AMP as the first choice for the UTI treatment [13]. In contrast, as was revealed in the present study, these two antibiotics cannot serve as treatments of choice in our region. A recent report which was made by Farshad et al., [14] also indicated that COT and AMP were not suitable drugs of

Resistance pattern	No. of isolates
AMP, AMX, GEN, TOB, CN,CTR, CAZ, CTX, NA, CIP, LOM, OF, COT	1
AMP, AMX, AK, GEN, TOB, CN, CTR, CAZ, CTX, NA, CIP, LOM, COT	1
AMP, AMX, NA, COT	3
AMP, AMX, GEN, CN, CTX, NA, LOM, OF, COT	1
AMP, AMX, CN, CTR, CAZ ,CTX, NA, CIP, LOM, OF, COT	1
AMP, AMX, AK ,GEN, TOB, CN, CTR, CAZ, CTX, NA, CIP, COT	1
AMP, AMX , AK, GEN, TOB , CN, CTR ,CAZ ,CTX, NA, CIP, COT, NF	1
AMP, AMX, AK, GEN, TOB, CN, CTR, CAZ, CTX, NA, CIP, LOM, OF	1
AMP, AMX	2
AMP, AMX, CN, CTR, CAZ, CTX, NA, CIP, LOM, OF, COT	2
AMP, AMX, AK , CN,CTR, CAZ, CTX, NA, CIP, LE ,LOM, OF, COT, NF	1
AMP, AMX, CN, CTR, CTX, NA, CIP, LOM, COT	1
AMP, AMX, NA, CIP, LE ,LOM, OF, COT	1
AMP, AMX, CN ,CTX , NA, CIP, LOM, OF, COT	1
AMP, AMX, AK, GEN, TOB , CN, CTR, CAZ, CTX , NA, CIP, LOM, OF, COT	3
AMP, AMX, CN,CTR, CAZ, CTX, NA, CIP, LOM, OF	1
AMP, AMX, CN ,CTR, CAZ, CTX, NA ,CIP, LOM, COT	2
AMP, AMX, CN ,CTR ,CAZ ,CTX , NA, CIP, LE, LOM, OF,COT	2
AMP, AMX, CN,NA ,CIP ,LE, LOM ,OF, COT, NF	1
AMP, AMX, NA	1
AMP, AMX , CN ,CTX , NA	1
AMP ,AMX, CN ,NA ,CIP ,LOM ,OF ,COT	2
AMP ,AMX , TOB , CN ,CTR ,CAZ ,CTX , NA ,CIP, LOM ,COT	1
AMP ,AMX , TOB , CN ,CTX , NA ,CIP,LOM ,OF ,COT	1
AMP ,AMX ,CN ,NA ,CIP, LE ,LOM ,OF ,COT	1
AMP ,AMX, NA, CIP ,LOM ,COT	1
AMP, AMX , GEN , CN, CTR ,CAZ ,CTX, NA, CIP ,LOM, OF, COT	1
AMP ,AMX, TOB, CN ,CTR ,CAZ ,CTX , NA, CIP, LOM, OF	1
AMP,AMX, AK,GEN, TOB, CN,CTR,CAZ, CTX, NA ,CIP ,LE ,LOM, OF, COT	2
AMP, AMX , TOB , CN, CTR ,CAZ ,CTX , NA, CIP ,LE ,LOM ,OF, COT	1

[Table/Fig. 3]: Resistance patterns of the uropathogenic *E. coli* isolates



[Table/Fig-4]: Increase in zone of inhibition diameter (≥5 mm) of three different patient isolate (a) in presence of CAC with respect to CAZ and CEC with respect to CTX respectively, (b) in presence of CEC with respect to CTX and (c) no change in zone of inhibition diameter when tested in presence of drug and drug-inhibitor combination disks. (a), (b) confirming ESBL phenotype, (c) non-ESBL phenotype respectively. All drug susceptibility tests were done in triplicate.

Antibiotics	ESBL producing E. coli isolates (n =18)	
	Resistant (%)	Intermediate(%)
AK	4(22.2)	1(5.6)
GEN	9(50)	4(22.2)
TOB	8(44.4)	2(11.1)
NA	18(100)	0
CIP	18(100)	0
LE	5(27.8)	5(27.8)
LOM	17(94.5)	1(5.6)
OF	12(66.7)	6(33.3)
COT	17(94.5)	0
NIF	0	4(22.2)

[Table/Fig 5]: Antibiotic resistance amongst the phenotypically confirmed ESBL producers

Resistance pattern	No. of isolates
GEN, TOB, NA, CIP, LOM, OF, COT	2
AK, GEN, TOB, NA, LOM, COT	1
NA, CIP, LOM, OF, COT	3
AK, GEN, TOB, NA, CIP, COT	1
NA, LOM, COT	1
GEN, NA, CIP, LOM, COT	2
NA, CIP, LOM, COT	1
GEN, NA, CIP, LE, LOM, OF, COT	2
TOB, NA, CIP, LOM, COT	1
GEN, TOB, NA, CIP, LE, LOM, OF, COT	1
AK, GEN, TOB, NA, CIP, LE, LOM, OF, COT	2

[**Table/Fig.6]:** Antimicrobial resistance pattern observed in the ESBL producers

choice for treating UTIs. However Shao et al., [15] have shown that AK and NF were the most effective treatments for UTIs in China. Our results also indicated similar sensitivity patterns amongst the uropathogens which circulated in Kolkata, an eastern region of India, against the following drugs. Thus, AK and NF could be used as effective therapies in our area.

The second and the third generation cephalosporins were very effective in the therapy of the infections which were caused by gram negative bacteria. However, in recent years, a number of authors have reported the advent of the CTX-M type Extended Spectrum Beta-Lactamases (ESBLs) worldwide [16]. Outbreaks of the infections which were caused by ESBL-producing organisms had been reported from virtually every European country [17]. Here, we are reporting the considerable rate of resistance to CTX; 67.5%, CTR; 62.5% and CAZ; 55% amongst the uropathogens which were studied, which could have been the result of the acquisition of genes for ESBL. The phenotypic confirmation test revealed that the ESBL production was 45% in the *E. coli* isolates which were tested in this study. The reported prevalence of the ESBL-producing gram-negative isolates in various hospitals in India was in the range of 19–60% [18]. A study which was performed in a tertiary care hospital in Hyderabad by Subbalaxmi et al., [19] showed that only 8% *E. coli* isolates were sensitive to CTR, a frequently used empirical antibiotic. However, our study indicated that CAZ was a better option as a high level of resistance was observed against CTX as well as CTR amongst the three cephalosporin drugs which were tested. Unfortunately, the increasing levels of ESBLs are reducing the clinical utility of this class of antibiotics due to the empirical administration of this class of drugs. Routine urine culture-sensitivity tests must be requested by the physicians in order to preserve these effective antimicrobials. Our study had limitations. A limited number of *E. coli* isolates were analyzed and their number must be increased, in order to further characterize the MDR isolates in detail. The hospitalization durations were not recorded and hence it was not possible to distinguish between the health care-associated infections and the community-acquired infections. However, such studies must be initiated from the eastern region of India, in order to gain an insight into the antibiotic susceptibility profile amongst the uropathogenic *E. coli* which circulate in this part of the country and comparisons must be made between the MDR isolates which are isolated from this region and from other parts of the country and worldwide.

CONCLUSION

It was quite alarming to note that almost all of the *E. coli* which were isolated in this study were found to be resistant to most of the routine antibiotics that were tested. Moreover, all the eighteen ESBL producers which were isolated were also multidrug resistant. Therefore, this is an important issue which has to be addressed by the policy makers, to formulate a strict antibiotic prescription policy in our country and region. Because the patterns of sensitivity of the microorganisms to the antibiotics vary over time and among different geographical locations, the empiric antibacterial therapy of the infections should be based on a local experience of the susceptibility and the resistance profile.

ACKNOWLEDGEMENTS

This work was carried out in the Department of Biochemistry and Medical Biotechnology, Calcutta School of Tropical Medicine, Kolkata, West Bengal, India and it was partly supported by a grant from the Department of Science and Technology, Government of West Bengal and by the R.D. Birla Smarak Kosh special research grant. The authors would like to thank Professor Krishnangshu Ray, Director of the Institute and Professor K.K. Haldar, Head of the Department of Microbiology for their kind cooperation and support.

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FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Aug 28, 2012**
Date of Peer Review: **Oct 31, 2012**
Date of Acceptance: **Nov 18, 2012**
Date of Publishing: **Mar 01, 2013**