Original Article

Prevalence of multidrug resistance and extended spectrum beta-lactamases among uropathogenic *Escherichia coli* isolates in a tertiary care hospital in South India: An alarming trend

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ABSTRACT

Background and Aims: *Escherichia coli* is the most common etiological agent in both community acquired and hospital acquired urinary tract infections. Emergence of multidrug resistance (MDR) among *E. coli* isolates is quite alarming. The aim of this study was to define the current prevalence of MDR and extended spectrum beta-lactamases (ESBL) production among *E. coli* isolates from urine samples in our hospital. **Materials and Methods:** Urine samples from 1225 patients were processed for wet mount followed by culture and sensitivity. All the samples were inoculated on to Hi Media Hi chrome agar plates (HiMedia Laboratories Pvt. Ltd., Mumbai, India) and growth showing significant bacteriuria ($\geq 10^5$ cfu/ml) were further identified by the standard biochemical procedures and antibiotic sensitivity done as per Clinical and Laboratory Standards Institute guidelines. Detection of ESBL was done by the combined disc method. Percentage of antibiotic resistance and sensitivity and Chi-square test were used. **Results:** Out of 1225 samples processed, significant bacterial isolates were obtained in 357 (29.1%). The total number of *E. coli* isolated were 179 (50.1%) of which multidrug resistant *E. coli* isolates were 148 (82.6%) and 71 (39.66%) were ESBL producers. High degree of resistance was observed to amoxycillin (93.2%) and amoxycillin-clavulanic acid (90.5%). More than 80% sensitivity was seen only to imipenem (98.4%), amikacin (83.3%) and nitrofurantoin (86.6%). **Conclusion:** Multidrug resistant strains of *E. coli* are widely prevalent in the community. Antibiotics like imipenem require hospitalization, parenteral administration, drug monitoring for toxicity, all of which incur high cost to the patient and have to be used judiciously.

Key words: *Escherichia coli,* extended spectrum beta-lactamases, multidrug resistance, urinary tract infection

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INTRODUCTION

About 150 million cases of urinary tract infections (UTIs) occur worldwide annually.[1] *Escherichia coli* is the most common organism found in community acquired as well as hospital acquired UTI. Inappropriate and widespread use of antibiotics has led to the emergence of drug resistance mechanisms like the production of extended spectrum beta-lactamases (ESBL), AmpC beta-lactamases, metallo-beta-lactamases and carbapenemases. Various studies have reported the production of ESBL and concomitant multidrug resistance (MDR) among uropathogenic *E. coli*.[2-4] This is

of grave concern as it affects the treatment modalities. An understanding of the resistance pattern of the local isolates is therefore essential.

Aim of the study

To identify the current prevalence of MDR and ESBL production among *E. coli* causing UTI in our hospital and to establish a regimen for the empirical treatment of UTI based on the drug sensitivity profile of the isolates in our hospital.

MATERIALS AND METHODS

Urine samples from 1225 patients received in the Microbiology Department of our hospital were processed for culture and sensitivity. Wet mount to detect the presence of pus cells and bacteria was done. All the samples were inoculated on to Hi Media Hi chrome agar plates (HiMedia Laboratories Pvt. Ltd., Mumbai, India) and incubated at 37°C for 18-24 h. *E. coli* growth denoting significant bacteriuria (colony count $\geq 10^5$ cfu/ml) was preliminarily identified by the purple colored colonies. Further identification was done by the standard biochemical procedures.

Antibiotic sensitivity was performed by the Kirby — Bauer disc diffusion method as per Clinical and Laboratory Standards Institute guidelines.[5] The isolates were tested against the following antibiotics: Amoxicillin, cefotaxime, cefoperazone, cefipime, imipenem, cefoperazone-sulbactam, pipericillin-tazobactam, amoxyclav, cotrimoxazole, amikacin, gentamicin, nitrofurantoin, norfloxacin and ciprofloxacin.

Multidrug resistance was defined as resistance to ≥one agent in each of ≥3 categories of antibiotics.[6]

Detection of ESBL was done by the combined disc diffusion method using ceftazidime and ceftazidime clavulanic acid. An increase in zone size of more than 5 mm was considered as positive for ESBL production.[7]

Statistical analysis

The percentage of sensitivity and resistance of the *E. coli* isolates to all the antibiotic classes was calculated [Table 1]. The difference in association between out-patients and in-patients with MDR was calculated using the Chi-square test. The Chi-square test was employed for calculating the significance of association of the ESBL strains with MDR. $P < 0.05$ was considered to be significant.

RESULTS

Of 1225 samples processed, isolates indicating significant bacterial UTI were obtained in 357 (29.1%) cases. The total number of *E. coli* isolated were 179 (50.1%). More number of females (56.9%) had significant UTI due to *E. coli* compared with males (43%). Maximum number of *E. coli* isolated was in the 18-65 years age group (70.95%) [Table 2].

Total numbers of multidrug resistant *E. coli* isolates were 148 (82.6%). Resistance to more than five and six drug classes comprised 63.51% of the total multidrug resistant strains. No significant difference was seen between out-patients and in-patients in causing MDR ($P = 0.375$).

High degree of resistance was observed to amoxycillin (93.2%), cefipime (91.62%) and amoxycillin-clavulanic acid (90.5%).

More than 80% sensitivity was seen only to imipenem (98.4%), amikacin (83.3%) and nitrofurantoin (86.6%).

Extended spectrum beta-lactamases production was detected in 71 *E. coli* isolates (39.66%) and all of them were multidrug resistant.

DISCUSSION

Urinary tract infection is one of the leading causes of morbidity among patients accounting for most of the out-patient visits and hospitalization. They are caused either by the ascending route from the urethra or via the descending route through

Table 1: Percentage of resistant *Escherichia coli* strains against various groups of antibiotics

Group of antibiotics	Class of antibiotic	Antibiotics used	Percentage of resistance
Group 1	Furadantins	Nitrofurantoin-Nf (300 μg)	13.4
Group 2	Folate pathway inhibitors	Cotrimoxazole-Co (25 μg)	62.01
Group 3	Quinolones	Nalidixic acid-Na (30 μg)	73.74
	Flouroquinolones	Ciprofloxacin-Cf (5 μg)	84.91
		Norfloxacin-Nx (10 μg)	77.65
Group 4	Aminoglycosides	Gentamicin-G (10 μg)	56.98
		Amikacin-Ak (10 μg)	16.7
Group 5	Aminopenicillins	Amoxicillin-Am (30 μg)	93.29
Group 6	Cephalosporins 3rd generation	Cefoperazone-Cs (75 μg)	75.97
		Cefotaxime-Ce (30 μg)	71.42
	Cephalosporins 4th generation	Cefepime-Cpm (30 μg)	91.62
Group 7	Beta-lactam+beta-lactamase inhibitors	Amoxyclav-Ac (20/10 μg)	90.53
		Cefoperazone-sulbactam-	75.41
		Pipericillin tazobactam-Pt (100 μg/10 μg)	41.89
Group 8	Carbapenems	Imipenem-I (10 μg)	1.67

the blood stream. The ascending route of infection accounts for more than 90% of the cases. The host factors contributing to the infection include female sex, sexual activity, use of spermicides and age.[8] The infective organisms are primarily derived from the fecal flora inhabiting the peri-urethral region. Uropathogenic *E. coli* is a heterogeneous group of strains of limited serogroups that constitute the primary pathogen in most of the UTI. The virulence factors of the organism encompass presence of adhesins, toxins, lipopolysaccharide, iron acquisition, presence of capsules and serum resistance.[9] Our study showed *E. coli* as the predominant agent accounting for nearly 45% of infections among in-patients and 50% of significant bacteriuria among the outpatients.

Females were more affected (56.9%) as expected as the well-known risk factors like shorter urethra, close proximity of the urethra to the perianal region and sexual activity predisposes females to UTI.

Nitrofurantoin, trimethoprim/sulfamethoxazole and fosfomycin are used for the empirical treatment of uncomplicated cystitis while flouroquinolones like ciprofloxacin, ofloxacin and norfloxacin are reserved as second line antibiotics. Beta-lactam antibiotics and amoxycillin-clavulanate are not recommended for first line treatment due to fears of resistance.[10] Our study showed a high degree of resistance to amoxycillin (93.29%), cotrimoxazole (62.01%), amoxyclav (90.53%) and all the quinolones (>73%) except nitrofurantoin (13.4%) [Table 2]. Nitrofurantoin is a widely available antibiotic which can be administered orally and is useful for uncomplicated lower UTI. Resistance to nitrofurantoin has been rarely reported among *E. coli* strains though a study done in Nagpur has cited 57.7% resistance to nitrofurantoin.[11] Studies by Zhanel *et al*.[12] and Karlowsky *et al*.[13] also have shown that urinary *E. coli* isolates exhibit a high degree of co-resistance to ampicillin and trimethoprim-sulfamethoxazole while resistance to nitrofurantoin appears to be unrelated to it.

Table 2: Patient demographic characteristics of UTI *Escherichia coli* isolates

Patient demographic characteristics	Number (%)
Sex	
Male	77 (43.1)
Female	102 (56.9)
Age	
≤17 years	35 (19.55)
18-64 years	127 (70.95)
≥65 years	17 (9.5)
Location	
Outpatient	97 (54.18)
Inpatient	82 (45.82)

UTI: Urinary tract infection

Multidrug resistant phenotypes

Sahm *et al*.[14] had reported a prevalence of 7.1% of MDR among urinary tract *E. coli* isolates in United States, with resistance to ampicillin, cephalothin and trimethoprim-sulfamethoxazole occurring as the predominant phenotype. We found a very high degree of MDR of 82.5% among our *E. coli* isolates. MDR to five drug groups (29.05%) was the predominant phenotype pattern followed by drug resistance to six or more antibiotics (23.46%) [Table 3]. A study conducted in Kolkata by Mukherjee *et al*.[15] showed MDR of 92.5% among uropathogenic *E. coli* with more than 90% resistance to amoxicillin, ampicillin and cephalexin and more than 80% strains resistant to cotrimoxazole and ciprofloxacin. Similar resistance pattern has been demonstrated in other studies across various countries. Hassan *et al*.[4] from Karachi had reported 94%, 85% and 60% resistance among urinary *E. coli* isolates to ampicillin, ciprofloxacin and gentamicin respectively while studies by Mowla *et al*.[3] from Bangladesh showed 92% and 50% resistance to ampicillin and ciprofloxacin. These data suggest that the problem of MDR is more rampant in the developing countries. Use of antibiotics in animal husbandry, self-medication, over the counter availability of antibiotics, dispensing them without proper prescriptions, nonadherence to antibiotic regimen by the patients and indiscriminate use even by clinicians all may act as contributory factors in the misuse of antibiotics and the subsequent development of MDR in this region. MDR can also be due to the spread of certain clonal groups of *E. coli*, which have similar virulence factors and antimicrobial sensitivity patterns.[16]

Escherichia coli and extended spectrum beta-lactamases production

Though *E. coli* rarely displays intrinsic resistance to antimicrobial drugs, plasmid mediated transferable drug resistance to one or more antibiotics is displayed by strains isolated from the normal flora of the general population. Occurrence of ESBL production in *E. coli* strains is important as they constitute a major part of the commensal flora

Table 3: Percentage of multidrug resistant isolates

MDR	Total number (%)	Outpatient (%)*	Inpatient (%)*	Number of ESBL isolates (%)†
Resistance to 3 drug groups	31 (17.31)	13 (7.26)	18 (10.05)	6 (3.35)
Resistance to 4 drug groups	23 (12.84)	13 (7.26)	10 (5.58)	13 (7.26)
Resistance to 5 drug groups	52 (29.05)	32 (17.87)	20 (11.17)	42 (23.46)
Resistance to ≥6 drug groups	42 (23.46)	22 (12.29)	20 (11.17)	10 (5.58)
Total number of MDR	148 (82.68)	80 (44.69)	68 (37.98)	71 (39.66)
Sensitive to all 8 drug classes	20 (11.17)	6 (3.35)	14 (7.82)	0

*No significant difference was seen between out-patients and in-patients in the occurrence of MDR ($P = 0.375$), †The association of ESBL production and MDR was found to be statistically significant by the Pearson's Chi-square test ($P = 0.0012$), ESBL: Extended spectrum beta lactamases, MDR: Multidrug resistance

of the intestines and thus serve as reservoir of infection in the c0ommunity. ESBL are generally Ambler class A beta-lactamases that have undergone mutations at critical aminoacids. The target amino acid residues where the mutations occur include Gly 238, Ala 237, Arg 164, Asp 179, Asp 104. Mutation occurring at position 238 wherein glycine is replaced by serine, alanine or aspartate is the most common. The mode of action is the structural remodeling of the active site of the beta-lactamases,[17] leading to hydrolysis of extended spectrum cephalosporins, all penicillins and monobactams. A study by Mekki *et al*.[18] had shown ESBL production among uropathogenic MDR *E. coli* as 53% compared to 39.66% in our study. In a study conducted by Mohammed *et al*.[19] at Aligarh, 34.42% of *E. coli* isolates causing UTI were ESBL producers.

Extended spectrum beta-lactamases and multidrug resistance: Challenges

The problems with emergence of ESBL producers are manifold. Firstly, as the ESBL trait is a transferable drug resistance usually mediated via plasmids, resistance genes to other agents like flouroquinolones, amino glycosides and trimethoprim-sulfamethoxazole are also transferred by conjugation. In a study by Baral *et al*.,[20] plasmid profiling of the MDR *E. coli* showed presence of single or multiple plasmids of sizes varying from 2 to 51 kb and a high frequency of conjugation of 1.5×10^{-7}. Conjugation experiments revealed that 85.7% of donor strains could transfer the ESBL MDR phenotype.

In our study, all the 71 ESBL *E. coli* isolates were multidrug resistant. The ESBL producing strains showed poor sensitivity to ciprofloxacin, ofloxacin (5.63% each), cotrimoxazole (11.26%) and gentamicin (40.84%). Moderate degree of sensitivity was seen to nitrofurantoin (73.23%) and amikacin (70.42%) [Table 4]. In most instances, these are the first line antibiotics for UTI and emergence of MDR necessitates a change in the choice of the empirical antimicrobial agents.

Second, it restricts the usage of beta-lactam and cephalosporin drugs which has got an extended spectrum of activity against Gram-positive and Gram-negative organisms and has low toxicity and better safety profile. Various studies have reported about the emergence of CTX-M type of beta-lactamases among the uropathogenic *E. coli* which has surpassed the TEM and SHV penicillinases and become the prevalent ESBL type.[21] Zhanel *et al*. had observed that 76.4% of ESBL producing *E. coli* strains demonstrated MDR phenotype with CTX-M being the predominant genotype.[12] The occurrence of CTX-M beta-lactamases has been linked to prior antibiotic therapy within 1-month preceding the current episode.

Table 4: Sensitivity of ESBL isolates to other antibiotics

Antibiotic	Total number of sensitive isolates	Percentage of sensitivity of ESBL isolates to antibiotics
Amikacin	50	70.42
Gentamicin	29	40.84
Nitrofurantoin	52	73.23
Norfloxacin	4	5.63
Ciprofloxacin	4	5.63
Imipenem	70	98.59
Cotrimoxazole	8	11.26

Total number of ESBL isolate = 71, ESBL: Extended spectrum beta-lactamases

Third, in conditions like pregnancy where the choice of antimicrobials is limited to beta-lactam antibiotics like ampicillin and cephalosporins, infections due to ESBL strains make the treatment difficult. The other antibiotics used are trimethoprim-sulfamethoxazole and nitrofurantoin. Nitrofurantoin achieves high urinary concentration but its tissue penetration is poor and cannot be used in complicated urinary infections.[22]

Multidrug resistance and treatment options

Carbapenems still remains as the antibiotic with highest sensitivity in ESBL *E. coli*. Doripenem is one of the newer carbapenem, which is advocated in complicated UTI.[23] Barring one strain, all the isolates in our study were sensitive to imipenem (98.59%). Increased prevalence of multidrug resistant ESBL *E. coli* would lead to an increase in the use of carbapenems. This would have a deleterious effect in that the production of carbapenemases by the bacteria would rise. It would be prudent to restrict the use of carbapenems to cases of complicated UTI or those having sepsis or for patients admitted in the intensive care units as their injudicious use may lead to the spread of carbapenemases and further limit the antibiotic armamentarium.

Aminoglycosides are the other group of antibiotics that have shown a good sensitivity profile (70.42%). The draw backs of using them include requirement for parenteral administration and low safety profile especially among the elderly. This can be overcome by opting for single day dosing or by using in combination with other antimicrobial agents.

In general, presence of ESBL trait renders the enzymes susceptible to inhibition by inactivators such as clavulanic acid, sulbactam and tazobactam. Peralta *et al*.[24] had suggested the use of beta-lactam/beta-lactamase inhibitors for empirical treatment or deescalating strategy in ESBL *E. coli* bacteremia patients. These CTX-M beta-lactamases are readily inactivated by clavulanate and tazobactam and less so by sulbactam favoring the use of oral amoxyclav as second line agents in the treatment of less serious cystitis infections.[25] In contrast, our data shows a high degree of *in vitro* resistance to amoxyclav (90.53%) and cefaperazone-sulbactam (75.41%) [Table 2]. This suggests the possibility of the existence of other beta-lactam resistant mechanisms. Further studies regarding the genotype of ESBL strains and their Minimum Inhibitory Concentrations will throw more light in this regard.

All these data indicate a widely prevalent MDR pattern to all the commonly used antibiotics and an urgent need to reconsider the antibiotic prescribing pattern. Restricting the use of antimicrobial agents will release the selection pressure on the bacteria and a reversal from the antibiotic resistant to sensitive state. This has been observed in the case of chloramphenicol resistance in *Salmonella typhi* wherein most of the strains have become sensitive to chloramphenicol once their use was discontinued.[26]

Other therapeutic options like using only nonsteroidal antiinflammatory drugs for symptomatic relief,[27] restricting the use of antibiotics for only 3-5 days,[10] use of cranberry juice, vaginal probiotics, antibiotic coated catheters and immunostimulatory agents[23] all can be explored so that antibiotic usage is restricted.

CONCLUSION

Multidrug resistant strains of *E. coli* are widely prevalent and isolation of the same in the community acquired UTI is a matter of grave concern. Our study shows a high degree of MDR (82.6%) of which more than 63% showed resistance to five and six groups of antibiotics and nearly 40% exhibited ESBL production. Most of these isolates including the ESBL strains were sensitive to only imipenem, nitrofurantoin and amikacin.

Antibiotics like imipenem require hospitalization, parenteral administration, drug monitoring for toxicity, all of which incurs high cost to the patient and cannot be used as the first line of treatment. Data from our study shows that nitrofurantoin still remains the preferred drug for empirical therapy of uncomplicated lower UTI and the use of amoxycillin, ciprofloxacin and cotrimoxazole and amoxycillin-clavulanate for treatment of UTI has to be reconsidered. Aminoglycosides like gentamicin and amikacin can be used in a single day dosing format after assessing the risk profile for the patients. Though a very low percentage of resistance to Imipenem has been reported, the threat of spread of carbapenemases still looms large. Hence, the use of carbapenems has to be restricted to complicated and long standing UTIs. Judicious use of antibiotics is the need of the hour to prevent spread of the multidrug resistant strains in the community.

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