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Distribution of class 1 and 2 integrons among multi drug resistant *Escherichia coli* isolated from hospitalized patients with urinary tract in Cairo, Egypt

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ABSTRACT

Resistance pattern was performed by the disc diffusion method for 320 urine specimens collected from urinary tract infection (UTI) patients. Plasmid DNA from multi drug resistant (MDR) isolated *E. coli* strains was tested for class 1 and 2 integrons by PCR compared to other isolated strains. *E. coli* was accounted for 58.75 % of all strains. Strains of *E. coli* were 100% resistant to ampicillin, amoxicillin, cephalexin and chloramphenicol. All strains contained multiple number of plasmids ranged from 3 to 6 and appeared in 84% of *E. coli* strains. *Int*1 gene yielded a DNA fragment of 1.9 kb upon amplification by PCR and represented in 56% of *E. coli* isolates. The strong association observed between plasmid profiles and drug resistance patterns suggest that plasmids have epidemiological significance. A relatively high occurrence of class 1 integrons in *E. coli* strains (54%) suggests a correlation between the MDR behavior and the presence of transferable elements of these strains. Imipenem, gemifloxacin and gentamicin could be used for initial therapy for MDR *E. coli* mediated UTIs. Such studies are essential to determine the current guidelines for empirical therapy regimens which vary by location and helpful in the establishment of effective infection control measures.

KEYWORDS

Urinary tract infections;
E. coli;
Multidrug-resistant (MDR) bacteria;
Risk factors;
PCR.

INTRODUCTION

Despite the widespread accessibility of antibiotics, Urinary tract infections (UTIs) remain the second most frequent community-acquired adult infection and the main cause for nosocomial infection[1]. It is a major public health problem in terms of morbidity and healthcare costs[2]. *Escherichia coli* is one of the main causes of nosocomial infections, especially in patients in intensive care units and the main cause of urinary tract pathogen in the developed world, accounting for 70-0% of uncomplicated UTIs[3].

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Antibiotics abuse in treatment of UTIs is the main cause of multidrug-resistant organisms that are commonly found in UTIs[4]. The frequency resistance of *E. coli* to β-lactam is increased worldwide[5]. During the last decade, resistance of *E. coli* and other Enterobacteriaceae has continued to develop, with decreasing susceptibility to first-line agents such as ampicillin, nitrofurantoin, co-trimoxazole and more recently, the fluoroquinolones such as ciprofloxacin and levofloxacin[6]. The European data showed that 30 to 50% of isolates are resistant to amoxicillin[7] and varies between 6 and 17% to fluoroquinolones with progressively increasing[8]. The introduction of quinolones in clinical practice has been associated with an increasing incidence of quinolone-resistant bacteria[9]. Recent data suggest that the frequency resistance of *E. coli* to antimicrobials is steadily increasing[10]. The massive use and inappropriate choice of antibiotics are considered the most significant factors for the development of bacterial resistance to antimicrobial drugs[11]. There are several factors and abnormalities of UTIs that interfere with its natural resistance to infections. These factors include sex and age[12], disease, hospitalization and obstruction[13]. Females are however believed to be more affected than males except at the extremes of life[14].

Understanding the molecular mechanism of resistance genes may contribute to the creation of new antimicrobial strategies as well as some preventive measures to stop further spreading of resistance determinants among the pathogens[15]. Many resistant genes, in bacterial genomes and in extra-chromosomal pieces of DNA encode different mechanisms of drug resistance[16]. Gene mutations can spread from cell to cell by mobile genetic elements such as plasmids, transposons and bacteriophages. The drug resistance character is most often encoded on plasmids, which can easily be transferred among isolates. Plasmids may affect bacterial virulence and antibiotic resistance and serve as epidemiological markers[17].

Integrons are naturally efficient recombination and expression systems able to capture genes as part of genetic elements known as gene cassettes[18]. Five integrons classes related to antibiotic resistance have been described based on the homology of their integrase genes[19]. Class 1 integrons are most commonly found in nosocomial and community environments, followed by class 2 integrons, other integrons classes being scarcely reported to date. Class 1 integrons are associated with lateral transfer of antibacterial resistance genes. Drug resistant genes located on integrons like structures are being increasingly reported worldwide[20].

Data on antimicrobial resistance in Egypt are sparse, especially for MDR *E. coli* strains. Thus, we sought to detect the antimicrobial susceptibility of clinical *E. coli* isolates from UTIs at different hospitals in Egypt. The aim of this study was to examine the antimicrobial drug resistance pattern and the frequency of plasmids as well as the relationship between antibiotic resistance, genotypes, and plasmids carriage of the MDR *E. coli* isolates in UTI patients to determine risk factors associated with this development.

Materials and mthods

Study population

The study population was drawn from patients admitted in Al-Husain (I), Qasr Elaine (II) and Ain Shams (III) University hospitals in Cairo, Egypt. Three hundred and twenty patients clinically diagnosed as having UTIs were involved in this study. They were made up of 157 (49.1%) males and 163 (50.9%) females and aged between 19-72 years. Patients with the following criteria were excluded: concomitant or prophylactic antimicrobial treatment within 7 days before the study; history of renal impairment (serum creatinine above the normal range); anatomic and functional urinary tract abnormalities, for example, urinary tract obstruction, known urolithiasis, urinary tract tumors, neurogenic bladder disturbances, indwelling urinary catheters or stents; and patients who did not give their informed consent. No blood cultures were obtained from the patients.

Sample collection

Urine specimens were collected from eligible patients in early morning mid-stream using sterile, wide mouthed glass bottles with screw cap tops during the period between July and November (2009). Samples were then kept in an ice-box until laboratory analysis. The time between sample collection and sample analysis did not exceed one hour.

Bacterial identification

Urine samples were inoculated on nutrient, blood

TABLE 1 : Oligonucleotide primes used in the PCR assay

Primer	Oligoneucleotide sequence (5' - 3')
Int 1-F	GGTCAAGGATCTGGATTTCG
Int 1-R	ACATGCGTGTAAATCATCGTC
Int 2-F	CACGGATATGCGACAAAAAGGT
Int 2-R	GTAGCAAACGAGTGACGAAATG

and MacConkey agar plates and incubated at 37°C for 18-24 h. Cultivation, isolation, and identification of isolates from urine samples were performed using the conventional bacteriological methods. The identification of the *E. coli* strains were confirmed according to the standard method described by Koneman et al.[21].

Antibiotic susceptibility testing

Bacterial susceptibility to antimicrobial agents was determined by the disk diffusion method using the Kirby-Bauer method and as recommended by National Committee for Clinical Laboratory Standards (NCCLS). All discs were obtained from (Oxoid, England). Inoculum was then diluted to final concentration of (5-/10^5 CFU/ml) and inoculated into Mueller-Hinton agar (Difco, Detroit, Mich). Zones of inhibition of = 18 mm were considered sensitive, 13-17mm intermediate and < 13 mm resistant. Significant bacterial infection was defined as the growth of $\geq 10^5$ CFU/ml of a single species cultured from urine. Confirmation of Extended spectrum β-lactamases (ESBL) -production was performed using the E test (AB BIODISK, Solna, Sweden) method with an ESBL strip containing ceftazidime with and without clavulanic acid and using NCCLS guidelines. Quality control was performed concurrently during the processing of specimens using American Type Culture Collection (ATCC) strains including *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *E. coli* ATCC 35218, and *P. aeruginosa* ATCC 27853.

Analysis of plasmid DNA

Plasmid extraction procedure was carried out according to the methods described by Ish-Horowitz and Burke[22]. Plasmid DNA was separated by horizontal electrophoresis in 1% agarose gels in a Tris-borate EDTA buffer at room temperature at 100 volt (50 mA). Gels were stained with 0.5 μg/ml of ethidium bromide for 30 min at room temperature. DNA bands were visualized and photograph was taken using a documentation system with UV transilluminator. Plasmids present in strains *E. coli* PDK-9, R1 and V517 were used as molecular weight standard.

TABLE 2 : Isolation of inpatient urinary isolates (*n* = 320) by age and gender in 3 different hospitals

Age range (years)	Males (%)			Females (%)			Total (%)
	I	II	III	I	II	III	
≤14	3 (1.84)	0 (0.0)	2(1.22)	1(0.64)	3(1.91)	-	9 (2.81)
15–50	22 (13.50)	8 (4.91)	21(12.88)	11(7.01)	24(15.29)	8(5.10)	94(29.38)
51–64	27 (16.56)	23 (14.11)	19(11.66)	30(19.11)	14(8.92)	21(13.38)	134(41.88)
≥65	19 (11.66)	14 (8.59)	5(3.07)	28(17.83)	7(4.46)	10(6.37)	83(25.94)
Total (%)		163 (50.9)			157 (49.1)		320 (100)

I, Al-Husain university hospital; II, Qasr Elaine university hospital; III, Ain Shams university hospital

PCR amplification

Detection of class 1 and class 2 integrons was performed by PCR. The primers used for detection of int1 and int2 genes by PCR method are presented in TABLE 1. A single colony of each isolate was suspended in 25μl of reaction mixer containing 2.5μl of 10x PCR, 1.5μl of 50mM MgCl2, 2μl of 2.5mM dNTP, 1μl of primer (forward and reverse) together with 1 unit of Taq DNA polymerase (5U/μl). Volume of the reaction mixture was adjusted by adding filtered deionised water. PCR assays were performed in a DNA thermal cycler (Perkin-Elmer Cetus, Emeryville, 480220/220 V. 50 Hz). Each PCR test used the same basic set-up: 94ºC for 12 min followed by 30 cycles of 1 min at 94ºC, 30 sec for annealing at (60ºC), 2 minutes at 72ºC for elongation and final extension was conducted at 72°C for 10 min. A reagent blank, which contained all components of the reaction mixture with the exception of the bacteria, was included in every PCR procedure. ATCC *E. coli* 25922 strain was used as negative control for all PCR. *E. coli* ur-31, and *E. coli* ur-60 were used as positive controls for *int*1, *int*2 gene respectively. Amplification products were subjected to horizontal gel electrophoresis in 1% agarose gel (type II, Sigma, USA) in TBE (Tris-borate EDTA) buffer at room temperature at 100 volt (50mA) for 1 h. DNA bands were visualized by staining the gel with ethidiumbromide (0.5μg/ml) for 30 min and photographed.

Statistical analysis

MDR was defined by resistance to at least 3 of the

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TABLE 3 : Total isolated pathogens isolated from UTIs from the 320 patient

Organism	Male	Female	Number of Isolates	% of total
E. coli	61 (32.45%)	127 (67.55%)	188	58.75
Klebsiella pneumoniae	32 (78.05%)	9 (21.95%)	41	12.81
Pseudomonas aeruginosa	28 (96.55%)	1 (3.45%)	29	9.06
Enterococcus spp.	9 (56.25%)	7 (43.75%)	16	5.00
Enterobacter cloacae	8 (72.73%)	3 (27.27%)	11	3.35
Proteus mirabilis	3 (30.00%)	7 (70.00%)	10	3.13
Staphylococcus aureus	6 (66.67%)	3 (33.33%)	9	2.81
Citrobacter spp.	2 (50.00%)	2 (50.00%)	4	1.25
Coagulase-negative staphylococci	1 (50.00%)	1 (50.00%)	2	0.63
Staphylococcus saprophyticus	2 (100.00%)	0 (0.00%)	2	0.63
Enterobacter aerogenes	0 (0.00%)	1 (100.00%)	1	0.31
Klebsiella spp.	1 (100.00%)	0 (0.00%)	1	0.31
Streptococcus agalactiae	0 (0.00%)	1 (100.00%)	1	0.31
Morganella morganii	1 (100.00%)	0 (0.00%)	1	0.31
Serratia marcescens	0 (0.00%)	1 (100.00%)	1	0.31
Providencia stuartii	1 (100.00%)	0 (0.00%)	1	0.31
Acinetobacter baumannii	1 (100.00%)	0 (0.00%)	1	0.31

used antimicrobial drugs. Susceptible controls were isolates showing sensitivity to all of the aforementioned drugs. All data were analyzed with SPSS software for Windows, version 11.0 (SPSS Inc., Chicago, IL). The significance of differences between resistance patterns of *E. coli* isolates from different hospitals was determined using the chi-square test. All p values were based on 2-tailed tests of significance with $p \geq 0.05$ is considered statistically significant.

RESULTS

During the study period a 320 urine specimens were collected from three different university hospitals in Cairo, Egypt. TABLE 2 showed the distribution of urinary isolates by age and gender.

E. coli was isolated from 188 cases, of which 67.6% (n = 127) were from female patients and 32.4% (n = 61) were from male patients. Among the female and male patients, respectively 56.0% (n = 75) and 52.1% (n = 25) cases belonged to the age group >51 years. The bacteriology of the inpatient urinary isolates is summarized in TABLE 3. *E. coli* represented 58.75 % of all isolates. The other isolates obtained were *Klebsiella pneumoniae* (12.81 %), *Pseudomonas aeruginosa* (9.06%), *Enterococcus* spp. (5.00%), *Enterobacter cloacae* (3.35%), *Proteus mirabilis* (3.13 %), *Staphylococcus aureus* (2.81%), *Citrobacter* spp. (1.25%). No significant differences in bacteriology were obtained between Al-Husain, Qasr Elaine or Ain Shams university hospitals.

TABLE 4 : Percentages of susceptible (S), intermediate (I) and resistant (R) *E. coli* strains from UTIs

Antimicrobial agent (µg)	Diffusion zone Breakpoint * (mm)	*E. coli* isolates (n =188)		
		S (%)	I (%)	R (%)
Ampicillin (10µg)	≤13	0 (0)	0 (0)	188 (100)
Ampicillin/sulbactam (10/10µg)	≤ 13	42 (22.34)	19 (10.11)	127 (67.06)
Amoxicillin (20µg)	≤ 13	0 (0)	0 (0)	188 (100)
Amoxicillin/clavulanate (20/10µg)	≤ 13	77 (40.96)	25 (13.30)	86 (45.74)
Cephalexin (30 µg)	≤ 14	0 (0)	0 (0)	188 (100)
Chloramphenicol (30µg)	≤ 12	0 (0)	0 (0)	188 (100)
Imipenem (10µg)	≤ 13	168 (89.36)	9 (4.79)	11(5.85)
Ciprofloxacin (5µg)	≤ 15	98 (52.13)	23 (12.23)	67 (35.64)
Erythromycin (15µg)	≤ 13	58 (30.85	37 (19.68)	93 (49.47)
Gentamicin (10µg)	≤ 12	101 (53.72)	36 (19.15)	51 (27.13)
Amikacin (30µg)	≤ 14	104 (55.32)	24 (12.77)	60 (31.91)
Nalidixic acid (30µg)	≤ 13	87 (46.28)	30 (15.96)	71 (37.77)
Nitrofurantoin (300µg)	≤ 12	61 (32.45)	29 (15.43)	98 (52.13)
Norfloxacin (5µg)	≤ 12	97 (51.60)	27 (14.36)	64 (34.04)
Ofloxacin (5µg)	≤ 12	95 (50.53)	30 (15.96)	63 (33.51)
Gemifloxacin (5µg)	≤ 15	112 (59.57)	25 (13.30)	51 (27.13)
Levofloxacin (5 µg)	≤ 12	99 (52.65)	32 (17.02)	57 (30.32)
SMX/TMP (1.25/23.75 µg)	≤ 12	68 (36.17)	11 (5.85)	131 (69.68)
Tetracycline (30µg)	≤ 14	73 (38.83)	34 (18.09)	149 (79.26)

***According to 2006 NCCLS guidelines**

Antibiotic resistance in *E. coli* isolates

TABLE 4 describes the resistance to commonly used antimicrobials against urinary isolates obtained from three different hospitals in Cairo, Egypt. The percentage of susceptible, intermediate and resistant isolates to each antimicrobial agent is outlined in TABLE 4. For the 188 *E. coli* isolates overall, resistance to ampicillin was (100% resistance), amoxicillin (100%), cephalexin (100%) and chloramphenicol (100%), followed by Tetracycline (79.3%), SMX/TMP (69.7%), ampicillin/sulbactam (67.1%), erythromycin (49.5 %), amoxicillin/clavulanate (45.7%), and to a lesser extent to nalidixic acid (37.8%), ciprofloxacin (35.6%) and norfloxacin (34%). The most effective drugs against *E. coli* were imipenem, gemifloxacin, amikacin, gentamicin and

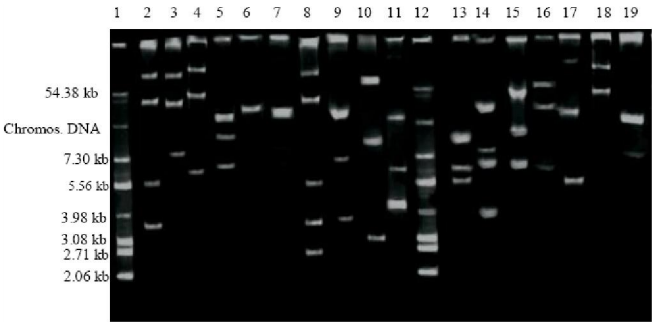

Figure 1 : Plasmid profile of standard strains and MDR *E.coli* clinical isolates. Lanes 1 and 12, standard plasmids from *E.coli* V-517; lanes 2-11 and 13-19 are clinical isolates of *E.coli*

levofloxacin. Resistance rates were higher in Al-Husain and Qasr Elaine hospitals compared with Ain Shams University hospital for all antimicrobials tested ($P < 0.05$).

Analysis of plasmid DNA and amplification of *Int*1 gene by PCR

Plasmid DNAs were analyzed in all resistant isolates by agarose gel electrophoresis which revealed that all theses isolates contained multiple numbers of plasmid ranging from 1 to 5. Size of isolated plasmid DNAs from clinical isolates was compared by standard plasmid from the reference strain *E. coli* V517 (sizes, 54, 5.6, 5.1, 3.9, 3.0, 2.7, and 2.1 kb). The migration distances of DNA bands were measured directly from photographs of the gels. Standard polynomial curves were generated with the logarithm of the relative migration of DNAs on the *x* axis and the logarithm of the molecular size of standard plasmids on the *y* axis with the Microsoft Excel program. Plasmid DNA was found to be present in 86% *E. coli* isolates (Figure 1). In a survey for the presence of class 1 integron in the isolated MDR strains mediating a urinary tract infection, PCR amplification of Int1 gene was conducted for all strains. In all tested isolates, amplified Int1 gene appeared as a DNA fragment of 1900 bp as expected. PCR test revealed that 105 isolates out of 188 (56%) of MDR *E. coli* harboring Int1 gene (Figure 2). However, Int2 gene was absent in tested MDR *E.coli* isolates (data not shown).

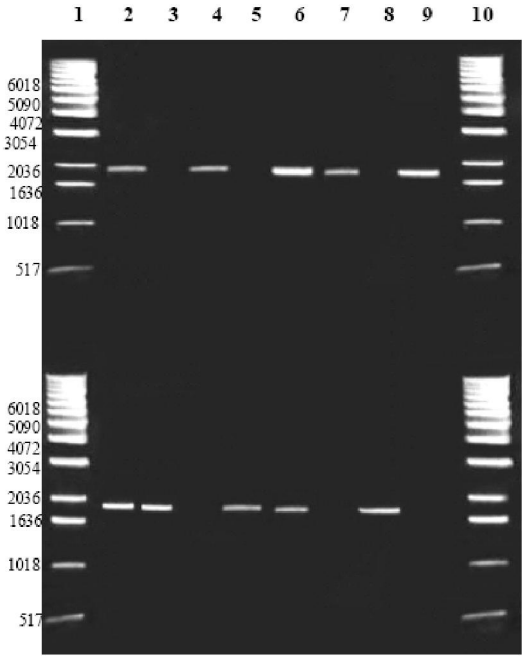

Figure 2 : PCR amplification of *Int1* gene among MDR strains. A fragment of 1.9kb was developed. Lanes: 1 and 12, fragments of DNA standard (0.07-12.2 kbs, Roche, Mannheim). Lanes: 2 in the upper panel, *E. coli* ur-31 as a positive control for *Int*1 gene; Lane 3 in the upper panel, *E. coli* ATCC 25922 strain as a positive control; Lanes 4-9 in the upper panel and 2-9 in the lower one, PCR of Int1 in the tested clinical isoltes. 3 µl of each sample was analyzed on 0.7% agarose gel

DISCUSSION

Multi drug resistant bacteria are now a problem in hospitalized patients throughout the world. The prevalence of MDR among clinical isolates vary greatly world wide and in geographic areas and are rapidly changing over time[23]. The occurrence of MDR producers in urinary isolates of *E.coli* in our study was found to be higher than reported in USA, Canada[24], and India[25]. This study examined the microbial spectrum of 320 urine specimens collected from UTI patients from three different hospitals in Cairo, Egypt. The results showed that *E. coli* was most frequent microorganism isolated from urine samples. Other investigators also reported that *E. coli* is the most commonly isolated aerobic microorganism from UTIs[26,27]. This study had been intended to examine the drug resistance pattern, the frequency of plasmids as well as the class1 integrons between the MDR *E. coli* isolates in UTI patients.

The antimicrobial resistance patterns of the isolated *E. coli* were studied. Of the 188 *E. coli* isolates characterized in this study, 100% displayed resistance to different antimicrobials, including penicillins, amoxicillin, cephalexin, and chloramphenicol. They showed variable pattern of resistance to tetracycline, SMX/TM,

erythromycin and quinolon group. These records are in accord with multiple previous studies suggesting use of these drugs has been a key factor in the emergence of antimicrobial resistant *E. coli*[28]. Increased resistance might attributed to lack of proper research, abuse of chemotherapeutic agents in Egyptian hospitals, public misuse of antibiotics and little or no preventive measure.

Most of the uropathogenic *E. coli* isolates (89.36%) were sensitive to imipenem. According to Franklin et al.[29], imipenem is most active agent against Gram-negative isolates, which correlates well with this study. To conclude if there was any correlation of UTIs with gender and age, the patient histories were analyzed and it was found that about 50.9% patient were females. It was previously found that UTIs is always a very common phenomenon among the women[30]. Women are mostly at risk of developing UTIs and half of all women develop a UTI during their lifetimes. Men and women of elderly group were found to be very much prone to UTI. In this study, about 56.0% female and 52.1% male cases belonged to the age group >51 years of age. It has been previously reported by several investigators that after middle age the incidence of UTI increases in men progressively owing to the development of prosthetic enlargement and consequent instrumentation[31]. In the present study, a much greater prevalence of this infection was observed in male and female at this stage of life.

The results of this study might reflect to the idea that the multiple antibiotic resistances among the isolates could be conferred by the plasmid and might be attributed from other organisms by any other gene transfer method. The multiple antimicrobial-resistant phenotypes observed in this study may have resulted from the spread of mobile genetic elements. For example, the observation that nearly 79.3% of ampicillin-resistant *E. coli* isolates were also resistant to tetracycline suggests resistance genes for these drugs are linked on plasmids. Moreover, the widespread resistance to SMX/TMP implies the presence of class I integrons, which are also important in conferring resistance to multiple antimicrobials.

Plasmid profile analysis give a clear vision about the appearance of plasmid associated with important phenotypic characteristics. Most importantly the antibiotic resistance character is most often encoded on plasmids, which can easily be transferred among isolates. Analysis of the plasmid DNA of *E. coli* isolates had shown that all the isolates tested contained multiple numbers of plasmids ranging from 1.0 to 5. Plasmid mediated multiple antibiotic resistance in different bacterial species are well recognized today. It appears from a previous study that the transferable resistance plasmid is the middle order plasmid having a molecular weight ranging between 44 and 76 kDa[32]. The present study showed that about 87% isolates were resistant to multiple antibiotics; of them 85% *E. coli* isolates harbored this middle order-ranged plasmid. The strong associations observed between plasmid profiles and drug resistance patterns suggested that plasmids may have epidemiological significance.

Mobilized integrons are substantial contributors to the spread of antibiotic resistance genes. The three classes of integron that mostly contribute to the problem of multidrug resistance are classes 1, 2, and 3[33], where classes are determined based on sequence differences in the respective Int1 proteins[34]. Of the three, class 1 integrons are the most abundant and are found in a diverse range of other mobile elements, such as transposons and plasmids. The antimicrobial resistant gene located on integron-like structure is being increasingly reported worldwide[35]. Presence of class 1 and class 2 integrons were also investigated in this study. Class 1 integron was observed in *E. coli* isolates (54%), but class 2 integron gave a negative results. Absence of *Int*2 gene may be attributed that class 2 integrons found in 4 to 20% of uropathogenic *Escherichia coli* strains[36] as well as in other human pathogens, other animal pathogens, and various commensal bacteria[37].

Previous studies had shown the association of the drug resistant genes with plasmids from bacteria responsible for nosocomial outbreaks, which were associated with class 1 integrons[38]. Class 1 integrons are frequently reported in clinical isolates of the family Enterobacteriaceae. As in other recent studies, resistance to quinolones was more common among integrons containing strains[30].

The results of this study showed a strong association between abuse of antibiotics and the emergence of resistance in *E. coli* from community acquired urinary tract infections. Wide spread use of these agents has

contributed to the rise of bacterial quinolone resistance. Fluoroquinolones should thus be used prudently, avoiding unnecessary prescriptions and considering alternative regimens for urinary tract infections. The widespread dissemination of MDR organisms would severely limit the therapeutic options of physicians facing these organisms, because the carbapenems are the only drugs uniformly active against these organisms. The increased risk of MDR *E. coli* in hospitalized patients could be considered a criterion for choosing an alternative therapy for community-acquired UTIs. It is important that these newer antimicrobial agents be used sparingly and with discretion. Furthermore, continuous monitoring of the antibiotic susceptibility of carbapenems is also necessary to check the effectiveness of this drug. The results of such study would be beneficial for determining guidelines for empirical therapy regimens. This is an important consideration, given the fact that an inappropriate choice of empirical antibiotics has been associated with poor outcomes and higher mortality rates in patients infected with *E. coli*.

CONCLUSION

Our study concludes that *E. coli* is one of the important causative agents of urinary tract infection in old men and women. Most of the isolates showed multiple antibiotic resistance, maximum resistance was found against ampicillin whereas, least resistance was detected against imipenem and hence it might be the drug of choice to treat UTI. Furthermore infection caused by the MDR organisms has currently been treated with carbapenems such as imipenem and meropenem. The results presented in this study could also help the establishment and enforcement of infection control measures.

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