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ORIGINAL ARTICLE

Detection of Extended Spectrum Beta-lactamase Producing *Escherichia coli* among Community-acquired and Hospital-acquired Urinary Tract Infections in Tanta University Hospital

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ABSTRACT

Background: *Urinary tract infection (UTI) is one of the most common hospital acquired and community acquired infections. Escherichia coli (E. coli) are the most prevalent bacteria causing UTI. As a result of the extensive use of β-lactam antibiotics in the clinical practice, extended spectrum β-lactamases (ESBLs) have emerged. E. coli is among the most prevalent ESBL producing bacteria.* ***Objectives*** *are to detect antibiotic sensitivity and ESBL production of E. coli isolates in hospital acquired and community acquired UTIs in Tanta University Hospital and to evaluate different methods for phenotypic confirmation of ESBL production.* ***Methodology:*** *E. coli isolates were identified by Conventional biochemical reactions. The isolates were tested for antibiotic sensitivity by the disc diffusion method. Different methods for phenotypic confirmation of ESBL production were evaluated.* ***Results:*** *E.coli was the causative organism in 58% of cases of community acquired UTI and 30% of cases of hospital acquired UTI. It was found that 37 of E.coli isolates were ESBL producers. Among the phenotypic confirmatory methods which were evaluated in our study, it was found that double disk synergy detected the least number of ESBL producing E.coli isolates.* ***Conclusions:*** *incidence of ESBL production among E. coli isolates is high. Periodical detection and monitoring of antimicrobial susceptibility of ESBL isolates, and rotating the use of effective antimicrobial drugs are recommended to decrease the risk of high antibiotic resistance rate.*

INTRODUCTION

Urinary tract infection (UTI) constitutes one of the most common infections for which patients seek medical attention [1]. If UTI left untreated , it can develop into very serious and potentially life threatening kidney infections that can permanently scar or damage the kidneys. In some adults, recurrent UTIs may cause scarring in the kidneys, which over time can lead to renal hypertension and eventual kidney failure [2].

Bacterial species are considered the most common cause of urinary tract infection. High burden of UTI is due to gram negative rods (80 to 85%) mainly *Escherichia coli* (*E.coli*) and *Klebsiella pneumoniae*[3].

Urinary tract infection is considered the most common infectious presentation in both hospital acquired and community acquired infections since long time. Community acquired and hospital-acquired UTIs differ with respect to aetiology, epidemiology and antibiotic susceptibility pattern[4,5].

Escherichia coli is the cause of 80-85% of community acquired UTI with *Staphylococcus saprophyticus* being the cause in 5-10%. Hospital acquired UTI are often associated with indwelling urinary catheters. These infections involve a much broader range of pathogens including: *Escherichia coli* 27%, *Klebsiella* 11%, *Pseudomonas* 11%, Fungi (*Candida albicans*) 9% and *Enterococci* 7%[6,7].

As a result of the extensive use of β-lactam antibiotics over the last several decades in the clinical practice, various β-lactamases have emerged. Extended spectrum β-lactamases (ESBLs) are the enzymes produced by Gram-negative bacilli that have the ability to hydrolyze β-lactam antibiotics (third generation cephalosporins and aztreonam) and are inhibited by β-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam[8].

ESBLs are usually plasmid-mediated enzymes. ESBLs are most commonly found in *Klebsiella pneumoniae* , *Escherichia coli* and other Gram-negative bacilli .They are a result of point mutations in B-lactamases encoded by bla TEM, bla SHV and bla CTX-M genes. In addition these plasmids also carry resistance to several other antimicrobial agents, an

important limitation in the design of treatment alternatives [9].

The presence of ESBL producing isolates is suggested if isolates showing resistance to expanded-spectrum cephalosporins or aztreonam. However further phenotypic confirmatory tests must be used to confirm the presence of ESBL production [10].

It was on this background the present study was conducted to detect the presence of extended spectrum beta-lactamase producing *Escherichia coli* in community-acquired and hospital-acquired urinary infections in Tanta University Hospital and to evaluate different methods for phenotypic confirmation of ESBL producing *Escherichia coli*.

METHODOLOGY

Patients:

The study was carried out in the Departments of Medical Microbiology & Immunology and Urology, Faculty of Medicine, Tanta University over 8 months period from March 2017 to October 2017 .This study included 100 patients ; 50 patients who attended to Urology Department Outpatient Clinics of Tanta University Hospital or inpatients who had UTI within their first 48 hours of hospital admission (Community acquired UTI group) and 50 patients who developed UTI after 48 hours of hospitalization who had no history of infection before hospital admission (hospital acquired UTI group). All individuals were subjected to complete history taking and clinical examination. Oral informed consents were obtained from the patients. The study was approved by the ethical committee of Tanta Faculty of Medicine.

Specimen collection:

Urine samples were obtained in sterile containers under aseptic precautions. Samples included mid stream urine for male and clean catch urine sample for female. In case of catheterized patients; the urine sample was collected through a sterile syringe after 10 min of clamping the catheter. The needle inserted proximal to the site of clamping under aseptic precautions.

Samples were transported as rapid as possible to the Medical Microbiology and Immunology department, Faculty of Medicine, Tanta University. If delayed the specimens were kept in the refrigerator up to 24 hours[11]. All collected urine samples were subjected to microscopic examination to detect the presence of pus cells, RBCs, crystals and casts.

Culture and identification of *E. coli* isolates:

Well mixed urine samples were cultured on cysteine lactose electrolyte deficient (CLED) and MacConkey's agar plates (Oxoid, UK), all plates were aerobically incubated overnight at 37ºC. The isolated colonies were identified morphologically regarding size, shape, surface, fermentation on CLED (figure1) and lactose fermentation on MacConkey's agar plates (figure 2). Films were prepared and stained with gram stain for detection of the morphology of the organism. Conventional biochemical reactions (triple sugar iron agar, Indole production, Citrate utilization and Urease production) using standard microbiological techniques were used for identification of *E. coli* isolates [12,13].

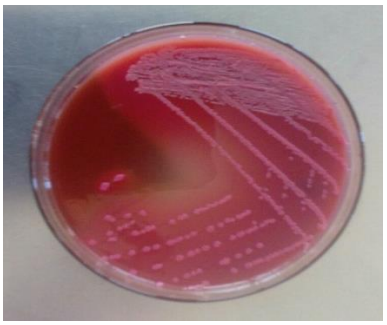

Fig. 1: Growth of *E.coli* as pink colonies on MacConkey's agar

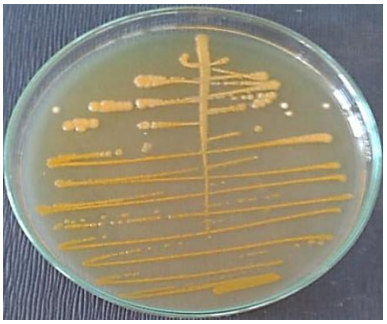

Fig. 2: Growth of *E.coli* as yellow colonies on CLED agar

Antimicrobial Susceptibility Testing of *E. coli* isolates:

Isolates biochemically identified as *E. coli* were subjected to antimicrobial susceptibility testing by the Bauer-Kirby disk diffusion technique, and interpreted in accordance with the guidelines established by the Clinical and Laboratory Standards Institute [14] using commercially available discs *(Oxoid ,UK)*: Ampicillin(10µg)**,**Ceftazidime (30µg)**,** Imipenem (10µg)**,** Meropenem (10µg), Amikacin (30µg)**,** Ciprofloxacin (5µg)**,** Norfloxacin (10 µg)}, Trimethoprim-sulfamethoxazole (25µg)**,** Nitrofurantoin (300 µg**)** (figure 3).

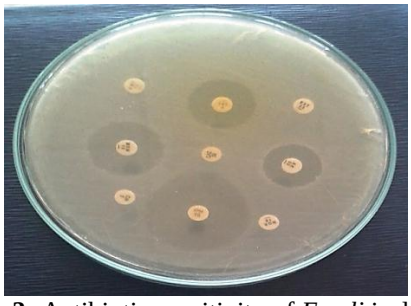

Fig. 3: Antibiotic sensitivity of *E.coli* isolates

Phenotypic tests for detection of ESBL producing *E. coli* isolates

ESBL screening test

According to CLSI guidelines of disk diffusion screening tests, *E. coli* isolates were considered potential ESBL producers if the diameter of zone of inhibition with Ceftazidime (30 µg) disk was ≤ 22[14].

Phenotypic confirmation of ESBL production by CLSI phenotypic confirmatory test (Combined disk method):

By using combined disks which were obtained from *(Oxoid ,UK*) and they included: The cefotaxime (30µg), cefotaxime-clavulanic acid (CCT, 30µg/10µg), ceftazidime (30 µg) and ceftazidime-clavulanic acid (CCA, 30µg/10µg) disks .The organism was interpreted as ESBL producer if there was an increase of ≥ 5 mm in the inhibition zone diameter of the combined disc when compared to the corresponding cephalosporin disc alone. The performance and interpretation were based on the recommendations of CLSI guidelines[14] (figure 4).

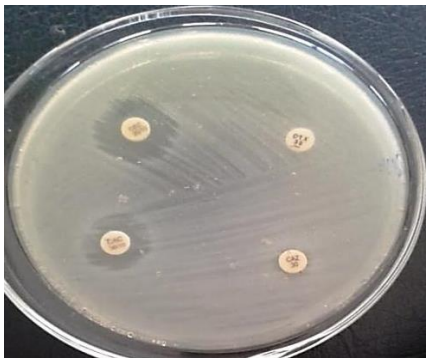

Fig. 4: Combined disk method showing an increase ≥ 5 mm in zone of inhibition of combined disks when compared to the corresponding cephalosporin disc alone

Evaluation of different methods for phenotypic confirmation of ESBL production

Double disk synergy test (DDST)

Disks of 3rd generation cephalosporin (ceftazidime 30µg, cefotaxime 30µg) or monobactam (aztreonam 30µg) were placed 30 mm apart (center to center) around an augmentin disk (20 µg amoxicillin /10 µg clavulanic acid) placed in the middle of inoculated Muller Hinton agar plate. Extension of the edge of the inhibition zone of ceftazidime, cefotaxime or aztreonam disks on the side exposed to the augmentin disk is considered positive for ESBL production. If the test was negative with 30mm distance, it was repeated placing the disks 20mm apart [15,16] (figure 5).

Fig. 5: Double disk synergy test showing extension of the edge of the inhibition zone towards the augmentin disk

Modified double disk synergy test (MDDST)

A disk of augmentin was placed in the center; then disks of ceftazidime (30µg), cefotaxime (30µg), aztreonam (30ug) and ceftriaxone (30µg) were kept around it at distance 15 mm from the augmentin disk (center to center). A cefoxitin disk (30ug) was also placed on the same plate (Oxoid,UK). Extension of the zone of inhibition between any of the ceftazidime, cefotaxime, ceftriaxone or aztreonam disks and AMC disk was interpreted as positive for ESBL production [17] (figure 6).

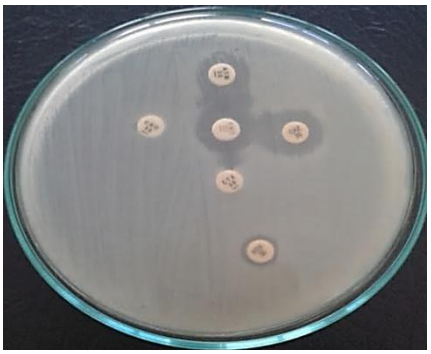

Fig. 6: Modified double disk synergy test showing extension of the edge of the inhibition zone towards the augmentin disk

C.ESBL E-Test

The E-test ESBL strips were obtained from (Liofilchem, Italy) and they included: E-test strip containing cefotaxime (MIC test range, 0.25–16µmg/L) at one end with cefotaxime plus clavulanic acid (MIC test range, 0.016–1µmg/L) at the other end was used and another strip containing cefepime (MIC test range, 0.25–16µmg/L) and cefepime plus clavulanic acid (MIC test range, 0.064–4µmg/L). A reduction of the MIC of cefotaxime or cefepime by three doubling dilutions in the presence of clavulanic acid (*i.e.*, MIC ratio of ≥8) was interpreted as confirmation of ESBL production. Deformation of ellipses or the presence of a keyhole zones 'phantom' were also considered as indication of

ESBL production even if the MIC ratio was <8 or cannot be read [18] (figure7).

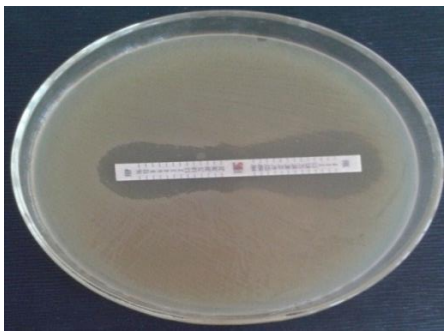

Fig. 7: Positive ESBL E-Test showing Deformation of the inhibition ellipses

Statistical Analysis:

Statistical presentation and analysis of the present study was conducted, using the mean, standard error, student t- test, Chi-square tests by SPSS V17.

RESULTS

The present study included 100 patients selected from out patients and inpatients who attended to Urology Department of Tanta University Hospital. Regarding sex distribution among patients, CAUTI group included 21 males and 29 females while HAUTI group included 24 males and 26 females (table 1).

Table 1: Sex distribution among patients of CAUTI and HAUTI groups

Sex		Group		Total
		CAUTI	HAUTI	
Male	N	21	24	45
	%	42	48	45
Female	N	29	26	55
	%	58	52	55
Total	N	50	50	100
	%	100	100	100
Chi-square	X^2	0.16		
	P-value	0.69		

As regards the distribution of *E.coli* among the collected urine samples of CAUTI and HAUTI groups, *E.coli* isolates were identified by conventional and biochemical methods in 58% of cases of CAUTI and 30% of cases of HAUTI with total percentage of 44% among the whole 100 urine samples which were included in this study (table 2).

Table 2: Distribution of *E.coli* isolates among CAUTI and HAUTI groups

Group	*E.coli* isolates	
	Number	%
CAUTI	29	58
HAUTI	15	30
Total	44	44

Antimicrobial susceptibility testing of *E. coli* isolates:

Antimicrobial susceptibility of E. coli isolates in CAUTI group:

The proportion of *E. coli* isolates showing resistance to ampicillin was 93.1% while the resistance rate to Ceftazidime was 86.2%. As regards imipenem and meropenem only 1 isolate (3.5%) was resistant to either one of them. Antimicrobial susceptibility to a panel of amikacin, ciprofloxacin, norfloxacin, trimethoprim-sulfamethoxazole and nitrofurantoin, was also tested. The percentages of resistance *E. coli* isolates to these antibiotics were 27.6%, 82.8%,75.9%,65.5% and 20.7% respectively (table 3).

Antimicrobial susceptibility of E. coli isolates in HAUTI group:

The proportion of *E. coli* isolates showing resistance to either ampicillin or Ceftazidime was 100%. As regards imipenem, meropenem only 2 isolates (13.3%) were resistant to imipenem while 3 isolates (20%) were resistant to meropenem. Antimicrobial susceptibility to a panel of amikacin, ciprofloxacin, norfloxacin, trimethoprim-sulfamethoxazole and nitrofurantoin, was also tested. The percentages of resistance *E. coli* isolates to these antibiotics were 33.3%,86.7%,86.7%,73.3% and 20% respectively (table 3).

Table 3: Antimicrobial susceptibility of *E. coli* isolates among CAUTI and HAUTI groups

Antibiotic	CAUTI				HAUTI			
	Sensitive cases		Resistant cases		Sensitive cases		Resistant cases	
	No	%	No	%	No	%	No	%
Ampicillin	2	6.9	27	93.1	-	0	15	100
Ceftazedime	4	13.8	25	86.2	-	0	15	100
Ciprofloxacin	5	17.2	24	82.8	2	13.3	13	86.7
Norfloxacin	7	24.1	22	75.9	2	13.3	13	86.7
Trimethoprim-sulfamethoxazole	10	34.5	19	65.5	4	26.7	11	73.3
Amikacin	21	72.4	8	27.6	10	66.7	5	33.3
Nitrofurantoin	23	79.3	6	20.7	12	80	3	20
Meropenem	28	96.5	1	3.5	12	80	3	20
Imipenem	28	96.5	1	3.5	13	86.7	2	13.3

By using CLSI phenotypic confirmatory test (Combined disk method) (14) , it was found that out of 44 *E.coli* isolates, 37(84%) isolates were phenotypically confirmed as ESBL producers .There were 24(82.7%) ESBL isolates out of 29 *E.coli* isolates in CAUTI group while there were 13(86.7%) ESBL isolates out of 15 *E.coli* isolates in HAUTI group (table 4).

Table 4: Distribution of ESBL producing *E.coli* among CAUTI and HAUTI groups

Groups		ESBL producing *E.coli*		Total
		+VE	-VE	
CAUTI	N	24	5	29
	%	82.7	17.3	100
HAUTI	N	13	2	15
	%	86.7	13.3	100
Total	N	37	7	44
	%	84	16	100

Comparison between different phenotypic confirmatory methods for detection of ESBL E.coli isolates:

The present study involved different phenotypic confirmatory methods for detection of the ESBL *E.coli* isolates including double disk synergy test, modified double disk synergy test and E-Test .It was found that double disk synergy detected the least number of ESBL *E.coli* isolates (20 isolates). Modified double disk synergy test detected 30 ESBL *E.coli* isolates. Regarding ESBL E-test, Cefepime/ Cefepime+Clavulanic acid E-test strip E-Test detected 33 ESBL *E.coli* isolates while Cefotaxime /Cefotaxime+Clavulanic acid E-test strip detected 28 ESBL *E.coli* isolates (table 5).

Table 5: **Comparison between different phenotypic confirmatory methods**

Method		DDS	MDDS	E-Test CTX/CTL	E-Test FEP/FEL
ESBL isolates detection	No.	20	30	28	33
	%	54	81.1	75.7	89.2

DDST: Double disk synergy test, **MDDST**: Modified Double Disc Synergy Test, **CTX/CTL**: Cefotaxime /Cefotaxime+Clavulanic acid E-test strip, **FEP/FEL**: Cefepime/Cefepime+Clavulanic acid E-test strip

DISCUSSION

The present study was carried out on 100 urine samples collected from out patients and inpatients who attended to Urology Department of Tanta University Hospital. Patients were divided in two groups including community acquired UTI (CAUTI) group and Hospital acquired UTI (HAUTI) group.

As regards sex distribution among patients who were included in the present study, 55% were females while 45% were males. Female patients represented 58% in CAUTI (group I) and 52% in HAUTI (group II).This indicates that the proportion of females was higher than males in both CAUTI and HAUTI groups. This finding is consistent with study done in India where female patients represented 63.89% and 61.71% in CAUTI and HAUTI groups respectively. This finding also is in accordance with a previous study done Egypt where female patients represented 71.43% and 73.53% in CAUTI and HAUTI groups respectively [19,20].

This finding is attributed to number of factors contribute to a greater prevalence of UTIs in females compared to males. These factors include that Female has shorter urethra with proximity to the anus that allows bacterial quick access to the bladder and the absence of antibacterial properties provided by prostatic fluid [21].

Regarding to the distribution of *E.coli* among the studied cases of CAUTI and HAUTI groups, the present study indicates that *E.coli* is the causative organism of 58% of cases of CAUTI and 30% of cases of HAUTI. This finding is in accordance with resuts of a previous study done in Egypt which reported that uropathogenic *Escherichia coli* (UPEC) are the primary cause of community acquired UTIs (70%) and a large portion of nosocomial UTIs (50%) [20].

By comparing the antimicrobial susceptibility of *E. coli* isolates of CAUTI group and HAUTI group in the present study, it was found that resistance rate of community acquired (CA) *E.coli* isolates to ampicillin, ceftazidime ,ciprofloxacin, norfloxacin, trimethoprim-sulfamethoxazole ,amikacin ,meropenem and imipenem was lower than resistance rate of hospital acquired (HA) *E. coli* isolates to those antibiotics (93.1versus 100%, 86.2%versus 100%, 82.8% versus 86,7%, 75.9 versus 86.7%, 65.5% versus 73.3%, 27.6 versus 33.3% ,3.5 versus 20% and 3.5% versus 13.3% respectively).This finding is consistent with results of previous studies done in India and Egypt which reported that resistance rate of the previously mentioned antibiotics was higher in HA *E. coli* isolates than in CA *E.coli* isolates[20,22,23]. As regards the proportion of resistance to nitrofurantoin in CAUTI and HAUTI ,they were almost equal (20.7 in CAUTI group versus 20% in HAUTI group).This result disagrees results of a previous study which reported higher resistance rate to nitrofurantoin in HAUTI group than in CAUTI group [23].

In the present study, imipenem was the least resistant antibiotic for both CA *E. coli* isolates and HA *E. coli* isolates (3.5% versus 13.3% respectively). In accordance with our results, Prakash and Saxena reported that the proportion of imipenem resistance in CA *E. coli* isolates was 7.74% and 15.48% in HA *E. coli* isolates [19].

In the present study, the ESBL positivity was detected in 37 (84%) out of *44 E. coli* isolates . This finding is consistent with results of *Fattouh et al* who reported that the proportion of ESBL producing *E. coli* isolates was (88.6%) [24]. This finding is higher than results of other studies done in Saudi Arabia and Pakistan which reported that proportion of ESBL *E. coli* isolates was 33.3% and 46.6 % respectively [25,26]. The present study indicated that there were 24 ESBL isolates (82.7%) out of 29 *E.coli* isolates in CAUTI group while there were 13 ESBL isolates (86.7%) out of 15 *E.coli* isolates in HAUTI group. This finding is in accordance with results of other studies done in Egypt which reported that ESBL *E.coli* isolates were higher in HAUTI group than in CAUTI group [20, 24].

In the present study, double disk synergy test (DDST) detected only 54% of ESBL isolates This result correlates with results of previous studies [27,28]. On the other hand this finding is lower than results of a previous study which reported that DDST detected 77.78% of ESBL isolates[29].

In the present study, modified double disk synergy test (MDDST) detected 81.1% of ESBL isolates. This finding correlates with a previous study done in India which reported that MDDST detected 86.8% of ESBL isolates [30]. On the other hand this finding was less than results of *Shaikh et al* who reported that MDDST had detected 95.23% of ESBL isolates[29].

The present study indicates that Cefotaxime/ Cefotaxime plus clavulanic acid (CTX/CTL) E test strip detected 75.7% of ESBL *E. coli* isolates in comparison with 89.2% ESBL *E.coli* isolates that could be detected by Cefepime/ Cefepime+Clavulanic acid (FEP/FEL) E test strip. This finding is consistent with results of a previous study which reported that CTX/CTL E test strip detected 71% of ESBL isolates while 90% of ESBL isolates were detected by FEP/FEL E test strip [31]. On the other hand these findings are lower than results of a previous study done in India which reported that CTX/CTL E test strip detected 88.5% of ESBL isolates while 91.8% of ESBL isolates were detected by FEP/FEL E test strip [30].

CONCLUSIONS

The present study indicated that *Escherichia coli* is the most prevalent causative organism of UTI and ESBL production among *E. coli* isolates is high in both community and hospital- acquired UTIs .Infections due to ESBL producing organisms are associated with limited response to many antibiotics as a result reliable detection of ESBL production by sensitive laboratory assays in clinical microbiology laboratory is essential to guide the clinicians to provide appropriate therapy. Periodical detection of ESBL isolates, monitoring their antimicrobial susceptibility, and rotating the use of effective antimicrobial drugs are recommended to decrease the risk of high antibiotic resistance rate.

Conflict of Interests

The authors stated that they have no conflict of interests.

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