Clinical and laboratory profiles of urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in a tertiary care center in central Saudi Arabia

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ABSTRACT

الأهداف: دراسة الخصائص السريرية والمخبرية لالتهابات المسالك البولية (UTIs) التي تسببها بكتيريا الاشيريكية القولونية (*E. coli*) المنتجة للبيتا لاكتاميز (ESBL) في المرضى الذين حضروا مستشفى الملك خالد الجامعي، ولتحديد المسببات والنتائج لإلتهابات البول لدى المرضى المصابين بالبكتيريا المنتجة والغير منتجه لهذا الإنزيم ومقارنة أنماط قابليتها للإستجابه للمضادات الحيوية المختلفة.

الطريقة: أجريت دراسة سريرية ومختبرية بأثر رجعي من يونيو 2009م إلى يونيو 2011م. تم دراسة 339 من البالغين والأطفال المرضى المصابين بالتهاب المسالك البولية. تم تقسيم المرضى إلى مجموعتين (مجموعة مصابة ببكتيريا الاشيريكية القولونية المنتجة للانزيم (ESBL) ومجموعة مصابة ببكتيريا غير منتجة لهذا اللإنزيم (non-ESBL *E. coli*). تم دراسة أعراض، وعلامات، ومضاعفات المرض، ونتائج تحليل البول، ومدى إستجابة البكتيريا للمضادات الحيوية.

النتائج: أظهرت نتائجنا أن من بين 339 مريض، 113 (33.3%) من الحالات مصابة بالاشريكية القولونية المنتجة للإنزيم (ESBL)، بينما 226 (66.7%) من الحالات مصابة بالاشريكية القولونية غير منتجة للإنزيم (ESBL). كان الأطفال أكثر شيوعاً للإصابة ببكتيريا غير منتجة للإنزيم. كما كان المرضى الإناث أكثر إصابة بالإشريكية القولونية ESBL. عوامل الخطر التي تم تحديدها للإصابة بالبكتيريا القولونية المنتجة للإنزيم (ESBL) شملت المرضى المصابين بأمراض الكلى وزراعة الكلى (p=0.017)، والأطفال ذوي ارتداد المثانة (p=0.044)، والتدخل الجراحي، والتهابات البول المتكررة (p<0.004) والمرضى المنومون. كان هناك فرق كبير في معدل الوفيات، مع المزيد من الوفيات التي تحدث في مجموعة البكتيريا القولونية ESBL. كانت البكتيريا المنتجة للإنزيم غالباً ما تكون مقاومة للمضادات الحيوية، بما في ذلك الجيل الثالث السيفالوسبورين، وجنتاميسين، وسيبروفلوكساسين، بينما غير ESBL كولاي كانت أكثر مقاومة للمضادات الحيوية التي ينصح بها عادة لعلاج التهاب المسالك البولية بما في ذلك الأمبيسيلين وكوترومكسازول.

خاتمة: تحديد عوامل الخطر وأنماط مقاومة مضادات الميكروبات المرتبطة بإنتاج الإنزيم ESBL لبكتيريا الاشريكية القولونية ضروري لاختيار العلاج المناسب بالمضادات الحيوية التجريبية لالتهابات البول.

Objectives: To study the clinical and laboratory characteristics of urinary tract infections (UTIs) caused by extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli (E. coli)*.

Methods: A retrospective clinical and laboratory study was performed at the Bacteriology Unit, Department of Pathology/Microbiology, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia from June 2009 to June 2011. A total of 339 adults and pediatric patients with UTI was included in the study. Two groups of patients (ESBL *E. coli* UTI and non-ESBL *E. coli* UTI) were studied. Symptoms and signs of illness, comorbidities, outcomes, and urine analysis results were analyzed.

Results. There was 339 episodes of culture-verified UTI, 113 (33.3%) cases were caused by ESBL *E. coli*, and 226 (66.7%) cases were caused by non-ESBL *E. coli*. Non-ESBL *E. coli* UTI was more commonly found in children, and ESBL *E. coli* was more predominant in female patients. Identified risk factors for acquisition of ESBL *E. coli* UTI included patients who had underlying renal disease and renal transplant (p=0.017), children with vesicoureteric reflux (p=0.044), surgical intervention, recurrent UTI (p<0.004), and in inpatients. Non-ESBL *E. coli* patients are more likely to present with UTI. The ESBL *E. coli* uropathogen are resistant to antibiotics, including the third generation cephalosporin, gentamicin, and ciprofloxacin, whereas the non-ESBL *E. coli* were more resistant to antibiotics Ampicillin and cotrimoxazole.

Conclusion: Identifying the risk factors and the antimicrobial resistance patterns associated with ESBL producing *E. coli* UTI is necessary for the development of an appropriate empirical antibiotic treatment.

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Urinary tract infection (UTI) is the second most common community acquired infection in clinical practice worldwide.[1] The antimicrobial resistance patterns of gram-negative organisms causing UTI have been changing over the years, including antimicrobial resistance due to extended-spectrum beta-lactamase (ESBL)-producing pathogens. The ESBLs are enzymes that mediate resistance to extended spectrum (third-generation) cephalosporins (for example; ceftazidime, cefotaxime, and ceftriaxone), and monobactams (for example; aztreonam) but do not affect cephamycins (for example; cefoxitin and cefotetan), or carbapenems (for example; meropenem, imipenem, and ertapenem). The presence of an ESBL-producing organism in severe infections can result in treatment failure if one of these classes of drugs is used.[2] The increasing prevalence of infections caused by antibiotic-resistant bacteria makes empirical treatment of these infections difficult. In addition, these infections cause serious complications, especially in patients with functional or structural anomalies of the urinary tract, patients who have undergone a kidney transplant, patients with polycystic kidneys, and patients with diabetes.[3] Data on the epidemiology of UTIs caused by ESBL-producing *Escherichia coli* (*E. coli)* are scant in published reports from the Kingdom of Saudi Arabia (KSA).[4,5] Most of those reports were studying the emergence and prevalence of ESBL producing *E. coli*/*Klebsiella pneumoniae* among urinary isolates with some focus on the risk factors. The aim of this study was to describe the epidemiology including the risk factors of UTIs, and to compare infections caused by ESBL-producing *E. coli* and non-ESBL strains. In addition, the antibiotic susceptibility pattern was also studied.

Methods. This retrospective study was conducted at the Bacteriology Unit, Department of Pathology/Microbiology, King Khalid University Hospital, Riyadh, KSA, a tertiary care medical center from June 2009 to June 2011. This work has been approved by the hospital ethics committee. The charts of children younger than 18 years old and adults with culture-verified UTI were reviewed. We recorded the gender, age, underlying disorders, findings of complete physical examinations, laboratory tests, urine culture results, and treatment type for each patient. Our criteria included hospitalized and outpatients UTI patients. An episode of UTI was identified by a positive urine culture performed by our microbiology laboratory. Identification of microbial growth and determination of antimicrobial susceptibility by the disk diffusion technique were performed according to the National Committee for Clinical Laboratory Standards with the recommended media and standard control strains.[6] Antimicrobial susceptibility was routinely tested against the following antimicrobial agents: nitrofurantoin; TrimethoprimSulfamethoxazole; representative aminoglycosides (gentamicin and amikacin); cephalosporins (cephalexin, cefuroxime, ceftazidime, cefotaxime, and ceftriaxone); aminopenicillins (amoxicillin and amoxicillin-clavulanate); ureidopenicillin (piperacillin); quinolones (nalidixic acid, ofloxacin, and ciprofloxacin); monobactam (aztreonam); and carbapenems (imipenem). The minimum inhibitory concentration (MIC) was recorded as the lowest concentration resulting in complete inhibition of growth. The *E. coli* isolates expressing an ESBL phenotype, as defined by a ceftazidime, cefotaxime, or aztreonam MIC of 2 g/mL or more were screened for ESBL production. The ESBL production was confirmed using the double-disk synergy test.[7] In brief, the *E. coli* was subcultured onto a Mueller Hinton agar plate (Saudi Prepared Media Laboratory (SPML), Riyadh, KSA) with an inoculum adjusted to a turbidity of 0.5 McFarland. A susceptibility disk containing amoxicillin clavulanate was placed in the center of the plate, and disks containing cefotaxime, ceftazidime, and aztreonam were placed 15-30 mm (center to center) from the amoxicillin clavulanate disk. After an overnight incubation, the clearing, enhanced inhibition, or truncated zones between the disk with clavulanic acid and that with ceftazidime, cefotaxime, or aztreonam were interpreted as a positive test. The methods for identifying ESBL-producing microorganisms were the same throughout the study period. No additional tests were carried out to fully characterize the clonal origin of the *E. coli* isolates. The patients were divided into 2 groups: an ESBL *E. coli*-UTI group and a non-ESBL *E. coli*-UTI group. The demographic features, underlying conditions, and antimicrobial susceptibilities of the UTI causative pathogens were compared between the 2 groups.

For statistical analysis, the Statistical Package for Social Sciences version 18 (SPSS Inc, Chicago, IL, USA) was used, and also the chi-square test and Fisher's exact test. A statistical significant difference was considered when $p<0.05$.

Results. A total of 233 children and 106 adults were enrolled in the study with 339 episodes of culture-verified UTI: 113 were caused by ESBL *E. coli*; and 226 were caused by non-ESBL *E. coli* ($p<0.0001$). There were 176 children and 50 adults diagnosed with non-ESBL *E. coli* UTI. The non-ESBL *E. coli* UTI

was more commonly found in children (p<0.0001). A total of 339 isolates from *E. coli* were isolated from 96 males and 243 females. The ESBL *E. coli* was more predominant in female patients (56%) compared to male patients (43%) (p<0.0001). A total of 77 patients were inpatients, and 262 patients were outpatients (p<0.0001). **Figure 1** shows the demographic features of the patients with ESBL *E. coli* versus the patients with non-ESBL *E. coli*. Underlying comorbidities were detected in 63 UTI episodes (19%) including renal disease, renal transplant, hydronephrosis, vesicoureteric reflux, neurogenic bladder, ectopic ureter, renal stones, urethral stricture, diabetes mellitus, hypertension, obesity, malignancy, autoimmune disease, and postsurgical. The ESBL *E. coli* UTIs were found more frequently in patients who had an underlying renal disease (p=0.017), and those who underwent renal transplant (p=0.017), children with vesicoureteric reflux (p=0.044), patients with post-surgical interventions (p<0.0001), patients with recurrent UTI (p<0.004) and inpatients (p<0.0001) (**Table 1**). Patients with non-ESBL *E. coli* UTI are more likely (p<0.0001) to present with UTI compared with ESBL *E. coli* UTI groups. There was a significant difference in the rate of death, with more deaths in the ESBL *E. coli* UTI group (p<0.0001) (**Table 2**). The ESBL *E. coli* uropathogen were often resistant to antibiotics, including the third-generation cephalosporin, gentamicin and ciprofloxacin (p<0.0001), whereas non-ESBL *E. coli* were resistant to antibiotics usually recommended for the initial therapy of UTIs including Ampicillin and cotrimoxazole (p<0.0001) (**Figure 2**).

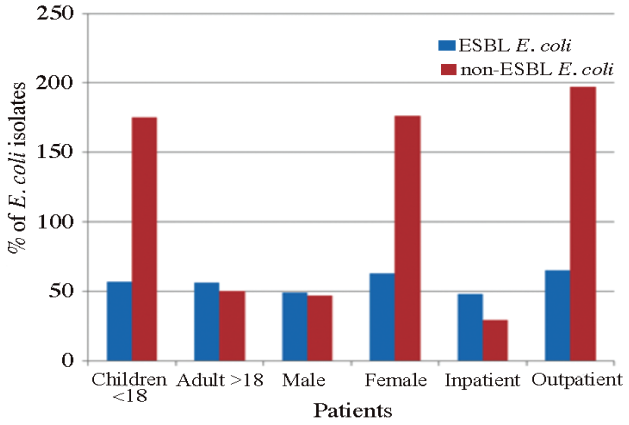

Figure 1 - Distribution of bacteria isolates according to patient age and gender, wards, and bacterial species (n=339). ESBL - extended-spectrum beta-lactamase, *E. coli - Escherichia coli*

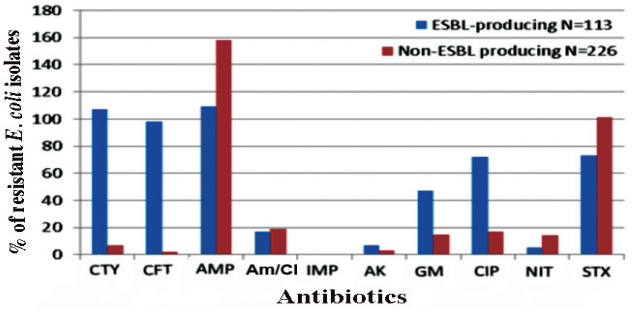

Figure 2 - Comparison of the antimicrobial susceptibility of non-extended and extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*). CTY - Cefotaxime, CFT - Ceftazidime, AMP - Ampicillin, Am/Cl - Amoxicillin/Clavulinic acid, IMP - Imipenem, AK - Amikacin, GM - Gentamicin, CIP - Ciprofloxacin, NIT - Nitrofurantoin, STX - Cotrimoxazole

Table 1 - Co-morbidities associated with extended-spectrum beta-lactamase (ESBL) and non-ESBL *Escherichia coli* (*E. coli*).

Co-morbidities	ESBL *E. coli* (N=113)		non-ESBL *E. coli* (N=226)		*P*-value
	n (%)				
Renal disease/renal transplant	10	(8.8)	3	(1.3)	0.017
Diabetes mellitus	1	(0.9)	3	(1.3)	0.593
Hypertension	1	(0.9)	1	(0.4)	0.556
Malignancy	3	(2.7)	1	(0.4)	0.208
Obesity	1	(0.9)	2	(0.9)	0.741
Renal stone	0	(0.0)	2	(0.9)	0.667
Autoimmune disease	1	(0.9)	3	(1.3)	0.593
Urethral stricture	0	(0.0)	2	(0.9)	0.444
Ectopic ureter	0	(0.0)	2	(0.9)	0.444
Hydronephrosis	0	(0.0)	2	(0.9)	0.444
Neurogenic bladder	4	(3.5)	8	(3.5)	0.633
Vesicoureteric reflux	5	(4.4)	2	(0.9)	0.044
Post surgical	8	(7.1)	0	(0.0)	<0.0001

Table 2 - Clinical infections due to extended-spectrum beta-lactamase (ESBL) and non-ESBL *Escherichia coli* (*E. coli*).

Variables	ESBL *E. coli* (N=113)		non-ESBL *E. coli* (N=226)		*P*-value
	n (%)				
Clinical infection due to ESBL microorganism					
Urinary tract infection	22	(19.5)	102	(45.1)	<0.0001
Recurrent urinary tract infection	13	(11.5)	8	(3.5)	0.004
Pyelonephritis	2	(1.8)	4	(1.8)	0.681
Clinical presentation					
Fever	10	(8.9)	24	(1.6)	0.609
Abdominal pain	2	(1.8)	7	(3.1)	0.375
Sepsis	0	(0.0)	1	(0.4)	0.667
Flank pain	1	(1.0)	7	(3.1)	0.192
Dysuria	2	(1.8)	10	(4.4)	0.176
Enuresis	0	(0.0)	3	(1.3)	0.295
Number of death	10	(8.9)	2	(0.9)	<0.0001

Discussion. Urinary tract infections cause a significant amount of morbidity and mortality. *Enterobacteriaceae* are the most common pathogens that causes UTIs, of these, *E. coli* is the most frequent, accounting for 65-90% of all UTIs.[3,8] The antimicrobial resistance patterns of organisms-causing UTI are changing over the years, including resistance due to ESBL-producing pathogens.[9,10] The current study aimed to determine the prevalence of antimicrobial resistance and ESBL production among *E. coli* isolates from patients with community and hospital acquired UTI. There are regional differences in the rate of ESBL producing *E. coli* reported worldwide.[4,8,11] The Pan European Antimicrobial Resistance using Local Surveillance (PEARLS) study[12] (2001-2002) showed that the percentages of ESBL production among *E. coli* was 5.4 % for all the study sites, and from KSA, the overall ESBL resistant rate from *Enterobacteriaceae* was 18.6%. Reports from KSA of ESBL producing *E. coli* showed variable results rates that ranged from 9.6-23%,[13,14] most of the *E. coli* isolates were uropathogens. In a recent study from India,[15] the ESBL positive *E. coli* uropathogens represented 52.2 % of the isolates.

In the present study, the ESBL positivity was detected in 33.3% of *E. coli* isolates. More than 50% (57%) of the ESBL producing *E. coli* isolates are of community origin. This rate is similar to that reported from Spain and other countries.[16,17] Unlike other studies that reported a higher prevalence of ESBL among isolates from children compared to adults,[10] in the current study, the non-ESBL *E. coli* was more commonly found in children. Consistent with other reports,[10,18] women represented most of the patients with a UTI. Female patients had a significantly higher risk of contracting UTIs caused by ESBL *E. coli* compared to male patients. Several studies have examined the antimicrobial resistance patterns of community-acquired ESBL *E. coli* UTI.[19-21] However, few studies have focused on community and nosocomial ESBL *E. coli* UTI.[18,22]

In the current study, the non-ESBL *E. coli* isolates were more resistant to antibiotics typically recommended for the initial therapy for UTI, including Ampicillin and trimethoprim-sulphamethoxazole, whereas ESBL *E. coli* uropathogens were often resistant to antibiotics including the third-generation cephalosporin, gentamicin, and ciprofloxacin; this pattern of antimicrobial resistance was similar to what has been reported by other studies in developing countries.[23-25] Multi-drug resistance was significantly higher in ESBL-producing *E. coli* compared to non-ESBL *E. coli*. The non-ESBL *E. coli* showed the greatest resistance to ampicillin followed by trimethoprim-sulphamethoxazole and ciprofloxacin. In agreement with previous reports,[10,25-27] the ESBL-producing *E. coli* isolates was significantly more resistant to trimethoprim-sulphamethoxazole, ciprofloxacin and third-generation cephalosporin compared to non-ESBL *E. coli*. This resistance did not affect imipenem.

An important worrisome finding in this study is the high rate of resistance (64%) to non-b-lactam antibiotics, particularly trimethoprim-sulphamethoxazole, ciprofloxacin, and gentamicin. Azap et al[26] reported antimicrobial resistance to trimethoprim-sulphamethoxazole, ciprofloxacin, and gentamicin in 39.2% of ESBL-producing isolates. Our findings of high rates of ESBL *E. coli* UTI prompted us to seek potential risk factors for this form of UTI. We identified 4 significant risk factors for ESBL *E. coli*: recurrent UTI cases ($p<0.004$); hospitalization ($p<0.0001$); surgical intervention ($p<0.0001$); and renal disease/renal transplant ($p=0.017$). Recurrent UTI, a major risk factor determined in our study for the prevalence of ESBL *E. coli*, was also found to be an independent risk factor in other studies from Turkey and Spain.[5,8,27] A well-designed, case-controlled study in Spain determined the epidemiology and clinical features of infections caused by ESBL-producing *E. coli* in 49 non-hospitalized patients. Most patients (76%) presented with UTIs, and the risk factors identified were: diabetes mellitus; previous fluoroquinolone use; recurrent UTIs; and previous hospital admission.[28]

The significant finding of a higher proportion of ESBL-producing isolates among *E. coli* isolates from inpatients compared to outpatients is similar to the observation by Khanfar et al,[5] and points to the possibility of nosocomial acquisition of UTI due to ESBL-producing pathogens. According to one study,[29] the risk factors associated with non-ESBL *E. coli* UTI resistance to first-line antibiotics are the use of antibiotics for >4 weeks in the previous 6 months, the presence of genitourinary abnormalities, hospitalization in the previous year, and an age older than 2 years old.

Our analysis is based on a retrospective study and has some limitations. First, the small sample size may indicate that other, less prevalent risk factors for ESBL *E. coli* infections went undetected. Second, measurements of predictor variables were obtained from clinical chart review that might be incomplete. Despite the above limitations, our study has shown the remarkable increase in the incidence of ESBL *E. coli* responsible for community-acquired UTI in the Saudi Arabian population. An important finding in our study was the determination of the risk factors for ESBL *E. coli* UTI.

A continued antibiotic multi-center surveillance to study the emerging problem of ESBL-associated UTI infection, and guide the selection of appropriate antimicrobial therapy in patients suspected of having UTIs caused by ESBL-producing *E. coli* is recommended.

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