Original Research Report

RISK FACTORS OF URINARY TRACT INFECTION CAUSED BY EXTENDED-SPECTRUM β-LACTAMASE-PRODUCING *Escherichia Coli* IN INPATIENTS AT A TERTIARY HOSPITAL IN SURABAYA, INDONESIA

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ABSTRAK

The incidence of urinary tract infections (UTIs) caused by extended-spectrum beta-lactamase (ESBL) producing Escherichia coli (E. coli) bacteria has become a global problem and has increased in recent years. The purpose of this study was to analyze the risk factors for the incidence of UTI in inpatients at Dr. Soetomo General Academic Hospital, Surabaya. This research was an analytic descriptive study. Specimens were sent to the Clinical Microbiology Laboratory using sterile containers and processed according to standard laboratory procedures. It resulted in ESBL-producing E. coli that were used as a case group and non ESBL-producing E. coli as a control group. The identification and testing of antibiotic susceptibility were carried out using the BD Phoenix™ Automated Microbiology System. Ninety-four bacterial isolates were collected, consisting of 54 (57.4%) ESBL-producing E. coli bacteria and 40 (42.6%) non ESBL-producing E. coli bacteria. Recurrent UTIs (OR = 4.31; ρ =0.002; 95% CI = 1.68-11.04) and catheter use (ρ = 0.049; OR = 4.250; 95% CI = 1.050-17.210) were used as independent risk factors caused by ESBL-producing E. coli bacteria. Recurrent UTIs and catheter use were dependent risk factors caused by ESBL-producing E. coli bacteria.

Keywords: *E.coli; extended-spectrum beta-lactamase ; urinary tract infections; risk factors; disease*

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Highlights:

1. ESBL frequency in women was higher than in men.
2. Catheter use in patients with urinary tract infections and recurrent urinary tract infections has four times the risk of ESBL caused by Escherichia coli bacteria
3. ESBL-producing E.coli bacteria are resistant to amoxicillin-clavulanic, ceftazidime, aztreonam, and ceftriaxone.

INTRODUCTION

Urinary tract infections (UTIs) represent microbial colonization and infection of urinary tract structures and are classified according to the site of infection into the kidney, bladder, and urethra (Sheerin 2011). UTI is one of the most common microbial diseases in a clinic, affecting all age groups (Kunin 1994). Globally, the prevalence of UTI is estimated at approximately 150 million people per year (Gupta et al. 2001). UTI is also one of the most common nosocomial infections, accounting for approximately 40% of all nosocomial bacterial infections worldwide (Mahamat et al. 2006). In Indonesia the incidence of UTIs is approximately 180,000 new cases annually (Sugianli et al. 2020). *Escherichia coli* (*E. coli*) is the most prevalent nosocomial pathogen (Ejrnæs 2011). Beta-lactamase risk factors were 83.3% in UTI isolates, 72.7% in urinary catheter use, and 65.3% before admission to ICU and use of antibiotics within 3 months (Sheik et al. 2016). Appropriate UTI management should be implemented to avoid recurrence and possible complications, also to prevent persistent bacteriuria, bacteremia, and urosepsis. Recurrent UTIs can lead to acute necrotizing renal infections. The presence of bacterial mutations that cause UTIs at different times and places allows for the presence of antimicrobial-resistance (AMR) bacteria Vranicianu (Tonolini 2018).

E. coli is responsible for 70-95% of UTI cases (Behzadi, P et al. 2010). Over 90% of ESBL-producing *E. coli* are susceptible to antibiotics such as tigecycline, amikacin, meropenem, ertapenem, and doripenem (Dahesihdewi et al. 2019). Several risk factors for infection with ESBL-producing bacteria have been identified, such as aginal infections, HIV/AIDS, immune system disorders, etc. (Uswanas et al. 2022; McLellan 2016).

Over the past two decades, there has been a significant number of infections caused by bacteria expressing extended-spectrum β-lactamases (ESBLs) and carbapenemases (Logan and Weinstein, 2017). In particular, ESBL isolates have been found in humans (Ashiboe-Mensah 2016), animals, the environment (water and soil) (Runcharoen et al., 2017), meat, and even vegetables (Yang et al., 2019). Increase of ESBL is becoming more common as use and exposure to β-lactamase, especially cephalosporins, are selected for this phenotype. This has led to a vicious cycle of drug resistance and diminishing therapeutic efficacy. Increased use of cephalosporins has been associated with *E. coli* infections in swine (Hammerum et al., 2014) and the high frequency of ESBL-producing *E. coli* was directly associated with high consumption of the third or fourth cephalosporins (Andersen et al., 2015; Chen et al., 2019). The increasing prevalence of ESBLs and multidrug resistance caused by multiple classes of antibiotics in UTIs has led the authors to conduct a research on risk factors for UTIs caused by ESBL-producing bacteria at a tertiary hospital of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

MATERIALS AND METHODS

A cross-sectional study was conducted at Dr. Soetomo Hospital in Surabaya, Indonesia to investigate the characteristics and risk factors of patients diagnosed with ESBL-producing *E. coli* in the medical and surgery ward. Ninety-four *E. coli* isolates from hospitalized patients with UTIs were phenotypically assessed for ESBL production using semi-automatic Phoenix BD. Its automated susceptibility and identification testing system provides rapid, reliable, and accurate detection of known and emerging antimicrobial resistance.

Data collected from both electronic, questionnaire, and paper-based medical records included patients demographics (birth date, sex, admission ward), culture and susceptibility results, antibiotic therapy for 3 months, hospitalization during 12 months, transfer from another healthcare facility, urinary catheterization during 30 days, and comorbidities based on Charlson Comorbidity Score. These study subjects were patients aged ≥ 18 years with suspected UTIs treated at the medical and surgery ward, Dr. Soetomo Hospital for more than 48 hours. The study was conducted at the Clinical Microbiology Unit from March to July 2019. The first isolate culture results were used in this study. The ethics committee had approved this study as outlined in the ethics eligibility statement number 1095 / KEPK / IV / 2019.

Samples from urine specimens were identified and tested for antibiotic susceptibility using a semi-automatic BD Phoenix system that met the inclusion and exclusion criteria. Urine isolates of 1 µL are taken to be inoculated on MacConkey and blood agar mayo is streaked using a calibrated loop and incubated for 18-48 hours at 37°C with the growth of 10≥5 CFU/ml (colony forming units/mL) is considered positive Samples from urine specimens were identified and tested for antibiotic susceptibility using a semi-automatic BD Phoenix system that met the inclusion and exclusion criteria. Urine isolates of 1 µL are taken to be inoculated on MacConkey and blood agar mayo is streaked using a calibrated loop and incubated for 18-48 hours at 37°C with the growth of 10≥5 CFU/ml (colony forming units/mL) is considered positive culture as the result (Versalovic et al. 2011).

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 25 (IBM Co., Armonk, NY, USA). Risk factors for ESBL-producing *E. coli* UTI were identified by univariate analysis. The final model included confounding variables significant at a two-tailed P-value of <0.05. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association.

RESULTS

In this study, ninety-four *E. coli* were collected from patients' urine samples at the Clinical Microbiology Laboratory of Dr. Soetomo General Academic Hospital that consisted of 54 (57.4%) ESBL isolates and 40 (42.6%) non ESBL-producing isolates. The identification was done by using the semi-automatic BD Phoenix system. The BD Phoenix is a bacterial growth-based automated system for determining antibiotic resistance characteristics in various test panels (Jonas, D et al. 2021). Based on age, the youngest patient was 25 years old and the oldest was 86 years old, while the average age of 56.60 was identified as the producer of ESBL and the average age of 57.00 was not the producer of ESBL. Out of the 55-64 years, ESBL was identified in as many as 20 (21.27%) isolates, while non ESBL-producing were 13 (13.82%) isolates, with a total of 33 isolates. The frequency of *E. coli* isolates by sex consisted of 67 women (71.3%) isolates and 27 men (28.7%) isolates. ESBL-producing bacteria were 36 (38.29%) isolates in women and 18 (19.14%) isolates in men. Urine specimens in this study according to ward origin consisted of 68 from medical ward (72.3%) and 26 from surgical ward (27.7%) (Table 1).

Table 1. Frequency of ESBL-producing and non-ESBL-producing *E. coli* bacteria

Room	*E. coli* ESBL n(%)	*E. coli* non ESBL n(%)	Total n (%)
Wards Medical	40 (42.5)	28 (29.8)	68 (72.3)
Surgical	14 (14.9)	12 (12.8)	26 (27.7)
Total	54 (57.4)	40 (42.6)	94 (100)

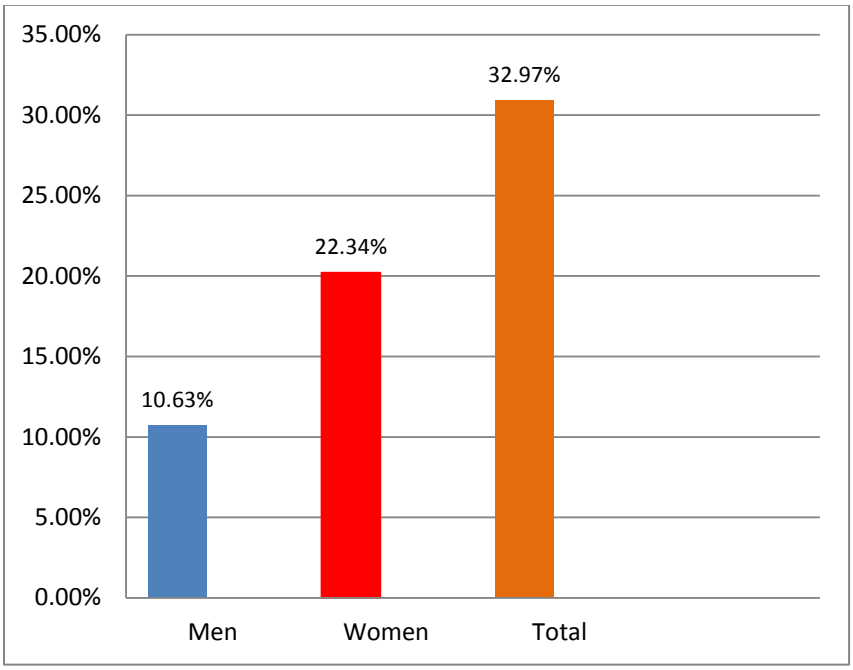

Figure 1. Frequency of UTI inpatients

Table 2. Antibiotic susceptibility to *E. coli* bacteria

	***E.coli* ESBL**			***E.coli* non ESBL**		
Antibiotic	S(%)	I(%)	R(%)	S(%)	I(%)	R(%)
Amikasin	54(57.4)			39(41.5)		1(1.1)
Gentamicin	38(40.4)		16(17)	36(38.3)		4(4.3)
Astreonam			54(57.4)	38(40.4)	1(1.1)	1(1.1)
Ampicillin Sulbactam			54(57.4)	15(16)	15(16)	10(10.6)
Amoxicillin clavulanate acid			54(57.4)	28(29.8)	10(10.6)	2(2.1)
Ampicillin			54(57.4)	11(11.7)		29(30.9)
Cefepime	3(3.2)		51(54.3)	36(38.3)	3(3.2)	1(1.1)
Piperacillin tazobactam	35 (37.2)	9(9.6)	10(10.6)	37(39.4)	2(2.1)	1(1.1)
Ceftazidim			54(57.4)	38(40.4)		2(2.1)
Cefotaxime			54(57.4)	38(40.4)		2(2.1)
Ceftriaxone	1(1.1)		53(56.4)	37(39.4)	1(1.1)	2(2.1)
Cefoperazon sulbactam	32(34)	14(14.9)	8(8.5)	36(38.3)	4(4.3)	
Trimethropin sulfametasol	16(17)		38(40.4)	19(20.2)	2(2.1)	19(20.2)
Tetracyclin	9(9.6)		45(47.9)	12(12.8)	1(1.1)	27(28.7)
Tigecycline	15(16)	1(1.1)	38(40.4)	33(35.1)	1(1.1)	6(6.4)
Ciprofloxacin	2(2.1)		52(55.3)	30(31.9)		10(10.6
Levofloxacin	3(3.2)		51(54.3)	30(31.9)		10(10.6)
Moxifloxacin	2(2.1)	1(1.1)	51(54.3)	30(31.9)		10(10.6)
Fosfomycin	44(46.8)	1(1.1)	9(9.6)	35(37.2)		5(5.30)
Nitrofurantoin	29(30.9)	13(13.8)	12(12.8)	37(39.4)	1(1.1)	2(2.1)
Meropenem	51(54.3)		3(3.2)	39(41.5)		1(1.1)
Imipenem	48(51.1)	3(3.2)	3(3.2)	36(38.3)	1(1.1)	3(3.2)

Table 3. Univariate risk factors for UTIs of ESBL-producing *E.coli* bacteria and non-ESBL-producing *E. coli*

Risk factors	ESBL n (%)	Non-ESBL n (%)	ρ-value	OR; (CI 95%)
Sex				
Male	18(33.3)	9 (22.5)	0.359	1.722; 0.677-4.379
Female	36(66.7)	31(77.5)		
Age	57.48 ±13.2	55.40 ±15.2	0.467	1.011; 0.981-1.041
Hospitalization			0.167	2.571; 0.762-8.675
Yes	12(22.2)	4(10)		
No	42(77.8)	36(90)		
Catheter use			0.049	4.250; 1.050-17.210
Yes	51(94.4)	32(80)		
No	3(5.6)	8(20)		
Transfer from			0.637	1.325; 0.512-3.431
another healthcare	15(27.8)	9(22.5)		
Yes	39(72.2)	31(77.5)		
No				
Recurrent UTI			0.002	4.308;1.681- 11.037
Yes	28(51.9)	8(20)		
No	26(48.1)	32(80)		
Surgical procedure			0.157	0.475; 0.188-1.201
Yes	11(20.4)	14(35)		
No	43(79.6)	26(65)		
Malignancy			0.014	0.277; 0.099-0.772
Yes	7(13)	14(35)		
No	47(87)	26(65)		
Chemotherapy			0.454	0.529; 0.112-2.511
Yes	3(5.6)	4(10)		
No	51(94.4)	36(90)		
Chronic disease			0.458	1.467; 0.544-3.954
Yes	44(81.5)	30(75)		
No	10(18.5)	10(25)		

The frequency of *E. eoli* isolates based on patients diagnosed with UTI in this study was 31 (32.97%) isolates, consisting of 21 (22.34%) isolates from women and 10 (10.63%) isolates from men (Figure 1).

From the susceptibility test results (Table 2), there was antibiotic sensitivity of piperacillin-tazobactam, cefoperazone sulbactam, nitrofurontoin, amikacin, gentamicin, meropenem, imipenem, and phosphomycin between 30%-57% in the ESBL-producing *E. coli* bacteria, while in non ESBL-producing *E. coli* bacteria the sensitivity was ≤ 40%.

Based on demographic data and characteristics of *E. coli* bacterial isolates, univariate analysis, variables such as sex, age, previous hospitalization, transfer from other healthcare, catheter use, recurrent UTI, antibiotic use, surgical procedures, malignancies, and comorbidities showed that independent risk factors of ESBL in this study was the use of a catheter with ρ = 0.049 and recurrent UTIs ρ = 0.002 (Table 3).

DISCUSSION

Extended-spectrum β-lactamases are enzymes that mediate resistance to the newer β-lactam antibiotics. In 1980s, ESBL-producing organisms were first reported, shortly after the introduction of the oxyimino β-lactam agents, and have now become widespread all over the world.

These enzymes are produced by the members of the *Enterobacteriaceae* family, mainly *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

UTIs are a common infectious diseases around the world. However, the diagnosis and treatment of UTI by clinicians tend to be based on their experiences. In developing countries, guidelines for UTI treatment cannot always be referenced. Despite this situation, studies to utilize UTI guidelines and to properly manage UTI in developing countries have not been fully investigated.

UTI caused by resistant bacteria is becoming more prevalent. Few studies are available regarding community-onset UTIs caused by extended-spectrum β-lactamase (ESBL)-producing bacteria. Research on risk factors associated with UTIs caused by ESBL-producing bacteria, especially Gram-negative bacteria, has been widely validated in European countries (Colodner et al., 2004; Ena et al., 2006). The ninety-four *E.coli* isolates meeting the inclusion and exclusion criteria were 67 (71.3%) isolates from women and 27 (28.7%) isolates from men. As reported by Joseph et al. (2014), the number of *E. coli* isolates identified by

Tamegnon et al. (2016) was 74.7% in women and 25.3% in men, slightly lower than those in this study.

Prevalence of ESBL was 54 (57.44%) isolates and non-ESBL was 40 (42.55%) isolates. The total number of ESBL in women was 36 (38.29%) isolates and 18 (19.14%) isolates in men. The number of ESBL-producing *E. coli* isolates was up to 56%, the same as the study conducted in Pakistan by Kausar et al. (2014).

This study was identical to a previous study by Ben-Ami et al. (2009) which found that catheter use was a risk factor for infection with ESBL-producing *E. coli* (rate 3.3). The frequency of recurrent UTI in this study was 28 (51.9%) isolates, consisting of 26 (48.1%) isolates from women and 10 (10.63%) isolates from men. The number of ESBL-producing *E. coli* bacteria was identified in 10 (10.63%) female and 6 (6.38%) male patients with $\rho = 0.002$; OR 4,308; CI 1.681-11.037. Al Yousef et al. (2016) showed that there were four risk factors for ESBL-producing bacteria, one of which was recurrent UTI infection (Odds 2.93). Meanwhile, Al-Jamei et al. (2018) in Jordan studied about the prevalence and risk factors for ESBL (Odd 2.83).

The independent risk factor in this study was the use of indwelling urine catheters that increased the risk of ESBL caused by *E. coli* by 4 times with $\rho = 0.049$; OR 4.250; CI 1.050-17.210. Pitout et al. (2005) stated that the use of catheters increases the risk of UTIs caused by improper sterilization techniques and minimal expertise during installation which causes contamination. Brill et al. (2021) stated the use of certain catheters such as foley catheters plays an important role as a risk factor for ESBL through biofilm formation between the catheter and urethral mucosa.

Antibiotic sensitivity of piperacillin-tazobactam, cefoperazone sulbactam, nitrofurantoin, amikacin, gentamicin, meropenem, imipenem, and phosphomycin is between 30%-57% in ESBL-producing *E. coli* bacteria, while in non ESBL-producing *E. coli* the sensitivity is ≤40%.

This study showed that ESBL-producing *E. coli* bacteria were resistant to amoxicillin-clavulanic and third-generation cephalosporins, such as ceftazidime, aztreonam, and ceftriaxone. These results were similar to those obtained by Taneja et al. (2008) and Bourjilat et al. (2011). High antibiotic sensitivity in this study included amikacin at 57.4%, phosphomycin at 46.8%, meropenem at 54.3%, and imipenem at 51.1%, which had similarities to antibiotics in a study in Pakistan by Kausar et al. (2014).

Strength and limitation

This study can contribute to research on urinary tract infections by adding more evidence of the risk factors for the disease. However, as a hospital-based research, this study might have a limited sample size.

CONCLUSION

The prevalence of ESBL was 54 (57.44%) isolates and 40 (42.55%) isolates for non-ESBL. ESBL frequency was 36 (38.29%) isolates in women and 18 (19.14%) isolates in men. The frequency of UTI in this study was 31 (32.97%) isolates, consisting of 21 (22.34%) isolates from women and 10 (10.63%) isolates from men. Catheter use in patients with UTIs and recurrent UTIs has four times the risk of ESBL caused by *E. coli* bacteria. ESBL-producing *E. coli* bacteria are resistant to amoxicillin-clavulanic and third-generation cephalosporin, such as ceftazidime, aztreonam, and ceftriaxone.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

ISW and K was responsible for conceptualization, data collection, and providing analysis. EBW was responsible for investigation of the data, data collection, manuscript revision, and grammatical checks. K was responsible as the supervisor, corresponding author, and also involved in manuscript preparation and validation.

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