# FACTORS ASSOCIATED WITH EXTENDED SPECTRUM β-LACTAMASE PRODUCING *ESCHERICHIA COLI* IN COMMUNITY-ACQUIRED URINARY TRACT INFECTION AT HOSPITAL EMERGENCY DEPARTMENT, BANGKOK, THAILAND

Sorravit Savatmongkorngul[1], Pongsuree Poowarattanawiwit[1], Kittisak Sawanyawisuth[2,3] and Yuwares Sittichanbuncha[1]

[1]Emergency Medicine Department, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok; [2]Department of Medicine, Faculty of Medicine, [3]The Research Center in Back, Neck Other Joint Pain and Human Performance (BNOJPH), Khon Kaen University, Khon Kaen, Thailand

**Abstract.** Urinary tract infection or UTI is most commonly caused by *Escherichia coli*. This study investigated the prevalence of and risk factors for extended spectrum β-lactamase-producing (ESBL) *E. coli* in community-acquired UTI presenting at the Emergency Department, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. A retrospective review was conducted over a one-year period (2014) of case histories of patients over 15 years of age diagnosed with ($n$ = 159) and without culture-positive ($n$ = 249) ESBL *E. coli*. Backward stepwise multivariate logistic regression analysis revealed four independent risk factors for UTI caused by ESBL *E. coli*, namely, urinary catheter use, previous UTI in which ESBL *E. coli* was present, and previous use of antibiotics cephalosporin and penicillin. This information should be useful in devising future public health prevention and control programs for ESBL *E. coli*-associated community-acquired UTI.

**Keywords:** *Escherichia coli*, extended spectrum β-lactamase, risk factor, urinary tract infection

## INTRODUCTION

Urinary tract infection (UTI) is caused most commonly by *Escherichia coli* (Tenover *et al*, 1995). Community-acquired *E. coli* infection is treated with third-generation cephalosporins, such as ceftriazone. Although extended spectrum beta-lactamase-producing (ESBL) *E. coli* infections were found first in hospital settings (Bradford, 2001), it has appeared in the community as well (Pitout *et al*, 2005; Rodriguez-Baño and Paterson, 2006; Apisarnthanarak *et al*, 2008).

As with other drug resistant organisms, ESBL infection causes a higher rate of morbidity and mortality in all age groups (Fernández *et al*, 2012; Fan *et al*, 2014). Several risk factors for ESBL *E.*

Correspondence: Dr Yuwares Sittichanbuncha, Emergency Medicine Department, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.
E-mail: yuwares.sit@mahidol.ac.th

*coli* infection in the community setting have been recognized, *viz*, age > 60 years, female, diabetes, recurrent UTI and previous use of antibiotics, such as penicillin or cephalosporins (Rodríguez-Baño *et al*, 2004; Calbo *et al*, 2006; Rodríguez-Baño *et al*, 2008; Azap *et al*, 2010). However, there has been limited studies of risk factors associated with ESBL *E. coli* infection in community-acquired UTI in Asian countries, including Thailand. Thus, this study investigated such risk factors in Bangkok, Thailand, which should provide useful information for formulating effective control measures to minimize ESBL *E. coli* infection.

## MATERIALS AND METHODS

### Subjects

This was a retrospective study conducted between January 1 and December 31, 2012 at the Department of Emergency Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok. Patients over 15 years of age and who were diagnosed as having community-acquired UTI based on *E. coli*- positive cultures (≥ 100,000 colonies/ml) were enrolled. Exclusion criteria were subjects who had been admitted to hospital within the prior month or had urine culture positive for more than two type of micro-organisms. The study protocol was approved by the ethics committee, Mahidol University (MURA2013/562).

### Data collection

Clinical data of all patients enrolled were retrieved and data regarding baseline characteristics; namely age, gender, current medication, co-morbid diseases, urological data, urine culture and drug sensitivity, and treatment prescribed were recorded. History of recurrent UTI was defined as contracting UTI at least twice within the preceding six months or three times within one year. History of hospital admission, out-patient treatment, surgery, and antibiotic use during the 3-months period prior to the diagnosis of UTI also were noted.

### Statistical analysis

Comparisons of clinical factors between groups were analyzed using descriptive statistics. Univariate logistic regression analysis was used to identify significant factors associated with ESBL *E. coli* UTI, which subsequently were computed by backward stepwise multivariate logistic regression analysis. Data of the final model are presented as adjusted odds ratio, 95% confidence interval and *p*-value (significance at < 0.05). All analyses were performed using PASW Statistics 18 (IBM, Armonk, NY).

## RESULTS

Based on a deviation of 15% and confidence of 95%, at least 399 patients have to be included in the study. During the study period, there were 463 patients diagnosed with community-acquired UTI at the Department of Emergency Medicine, Ramathibodi Hospital, among whom, 55 were not included based on the exclusion criteria: hospitalization within one month prior of diagnosis ($n$ = 48), urine culture positive for both *E. coli* and ESBL *E. coli* ($n$ =5), and urine cultures positive for more than 2 organisms ($n$ = 2).

Patients enrolled included 159 (39%) with ESBL and 249 (61%) with non-ESBL *E.coli* UTI. The ESBL group has significantly higher proportion of patients > 70 years of age, male, suffering from chronic lung disease, on urinary catheters, with structural and functional urinary defects, suffering from repeated UTI caused by either *E. coli* or ESBL *E. coli*, and with

Table 1
Clinical features of patients with community-acquired extended spectrum beta-lactamase (ESBL) and non-ESBL *E. coli* urinary tract infection (UTI).

| Feature | Non-ESBL *E. coli* ($N = 249$) | ESBL *E. coli* ($N = 159$) | $p$-value |
|---|---|---|---|
| | No. of patients (%) | No. of patients (%) | |
| Age > 70 years | 174 (70) | 131 (83) | 0.005 |
| Male gender | 41 (16) | 41 (26) | 0.022 |
| Pregnancy | 1 (0.5)[a] | 1 (1)[a] | 0.684 |
| Immuno-compromised | 21 (8) | 15 (9) | 0.728 |
| HIV infection | 2 (1) | 2 (1) | 0.645 |
| On immunosuppressive therapy | 17 (7) | 9 (6) | 0.638 |
| On chemotherapy | 2 (1) | 4 (2) | 0.214 |
| **Co-morbid diseases** | | | |
| Coronary artery disease | 24 (10) | 20 (13) | 0.350 |
| Heart failure | 11 (4) | 11 (7) | 0.275 |
| Peripheral artery disease | 3 (1) | 3 (2) | 0.682 |
| Chronic lung disease | 10 (4) | 14 (9) | 0.045 |
| Connective tissue disease | 3 (1) | 7 (4) | 0.052 |
| Dementia | 9 (4) | 8 (5) | 0.485 |
| Cerebrovascular disease | 40 (16) | 34 (2) | 0.174 |
| Hemiparesis | 16 (6) | 16 (10) | 0.183 |
| Chronic kidney disease | 16 (6) | 11 (7) | 0.845 |
| Leukemia | 1 (0.5) | 0 (0) | 1.000 |
| Lymphoma | 3 (1) | 3 (2) | 0.682 |
| Solid tumor | 32 (13) | 31 (19) | 0.070 |
| Metastatic cancer | 23 (9) | 22 (14) | 0.326 |
| Cirrhosis | 7 (3) | 8 (5) | 0.245 |
| Diabetes | 93 (37) | 69 (43) | 0.223 |
| **Urological-related factors** | | | |
| On urinary catheter | 15 (6) | 32 (20) | <0.001 |
| Renal stone | 11 (4) | 4 (2) | 0.319 |
| Urinary structural defect | 21 (8) | 28 (18) | 0.005 |
| Urinary functional defect | 11 (4) | 18 (11) | 0.008 |
| Repeated UTI | 43 (17) | 57 (36) | <0.001 |
| Previous UTI with non-ESBL *E. coli* | 23 (9) | 30 (19) | 0.005 |
| Previous UTI with ESBL *E. coli* | 15 (6) | 37 (23) | <0.001 |
| Hospitalization | 26 (10) | 25 (16) | 0.116 |
| Out-patient visit | 185 (74) | 132 (83) | 0.039 |
| History of surgical operation | 4 (1) | 5 (3) | 0.320 |

[a]Calculated over female patients; 118 subjects in ESBL group and 208 patients in non-ESBL group.

previous out-patient visits (Table 1). The ESBL group also shows higher uses of carbapenem, cephalosporins, penicillin, and fluoroquinolones (Table 2).

Although there appears to be 19 significant factors associated with ESBL *E. coli*-related UTI as revealed by univariate logistic regression analysis (Table 3), using

Table 2
Previous medication use in patients with community-acquired extended spectrum beta-lactamase (ESBL) and non-ESBL *E. coli* urinary tract infection (UTI).

| Antibiotic | Non-ESBL *E. coli* (*N* = 249) | ESBL *E. coli* (*N* = 159) | *p*-value |
|---|---|---|---|
| | No. of patients (%) | No. of patients (%) | |
| Gentamicin | 0 (0) | 1 (1) | 0.390 |
| Amikacin | 1 (0.5) | 0 (0) | 1.000 |
| Ceftriaxone | 15 (6) | 22 (14) | 0.007 |
| Ceftazidime | 1 (0.5) | 5 (3) | 0.035 |
| Cafazolin | 0 (0) | 3 (2) | 0.059 |
| Dicloxacillin | 0 (0) | 3 (2) | 0.059 |
| Amoxycillin | 3 (1) | 2 (1) | 1.000 |
| Amoxy-clavulanic acid | 4 (1.61) | 12 (7) | 0.003 |
| Ertapenem | 6 (2) | 15 (9) | 0.002 |
| Imipenem | 1 (0.5) | 1 (1) | 1.000 |
| Meropenem | 4 (2) | 6 (4) | 0.197 |
| Azithromycin | 4 (2) | 2 (1) | 1.000 |
| Clarithromycin | 0 (0) | 3 (2) | 0.059 |
| Ciprofloxacin | 7 (3) | 7 (4) | 0.389 |
| Levofloxacin | 5 (2) | 13 (8) | 0.003 |
| Norfloxacin | 1 (0.5) | 2 (1) | 0.563 |
| Ofloxacin | 2 (1) | 6 (4) | 0.061 |
| Ampicillin-sulbactam | 1 (0.5) | 2 (1) | 0.563 |
| Piperacillin-Tazobactam | 2 (1) | 5 (3) | 0.115 |
| Trimethoprim-Sulphamethoxazole | 3 (1) | 4 (2) | 0.439 |
| Doxycycline | 0 (0) | 1 (1) | 0.390 |
| Clindamycin | 2 (1) | 3 (2) | 0.382 |
| Metronidazole | 2 (1) | 3 (2) | 0.382 |
| Vancomycin | 3 (1) | 3 (2) | 0.682 |
| **Drug group** | | | |
| Cephalosporins | 15 (6) | 29 (18) | <0.001 |
| Penicillin | 10 (4) | 22 (14) | <0.001 |
| Carbapenem | 8 (3) | 18 (11) | 0.001 |
| Macrolides | 4 (2) | 5 (3) | 0.320 |
| Fluoroquinolones | 14 (6) | 25 (16) | 0.001 |
| Anti-tuberculosis | 1 (0.5) | 3 (2) | 0.304 |
| Anti-fungal drugs | 1 (0.5) | 3 (1.89) | 0.304 |
| Anti-retroviral drugs | 2(1) | 3 (1.89) | 0.382 |

multivariate logistic regression analysis there are only four significant independent factors, namely, urinary catheter use, previous UTI with ESBL *E. coli*, and previous treatment with cephalosporin and penicillin (Table 4).

## DISCUSSION

The purpose of the study was to determine factors that are associated with risk of community-acquired ESBL *E.coli* UTI from examining case histories of

Table 3
Univariate logistic regression analysis of factors associated with community-acquired extended spectrum beta-lactamase (ESBL) *E. coli* urinary tract infection (UTI).

| Factor | Non-ESBL *E. coli* ($N$ = 249) | ESBL *E. coli* ($N$ = 159) | OR (95%CI) | $p$-value |
|---|---|---|---|---|
| | No. of patients (%) | No. of patients (%) | | |
| Age > 70 years | 174 (70) | 131 (82) | 2.02 (1.24-3.29) | 0.005 |
| Male gender | 41 (16) | 41 (26) | 1.76 (1.08-2.87) | 0.023 |
| Chronic lung disease | 10 (4) | 14 (9) | 2.31 (0.99-5.33) | 0.050 |
| On urinary catheter | 15 (6) | 32 (20) | 3.93 (2.05-7.53) | <0.001 |
| Urinary structural defect | 21 (8) | 28 (18) | 32 (1.27-4.25) | 0.006 |
| Urinary functional defect | 11 (4) | 18 (11) | 2.76 (1.27-6.02) | 0.011 |
| Repeated UTI | 43 (17) | 57 (36) | 2.68 (1.69-4.25) | <0.001 |
| Previous UTI with non-ESBL *E. coli* | 23 (9) | 30 (19) | 2.29 (1.27-4.10) | 0.006 |
| Previous UTI with ESBL *E. coli* | 15 (6) | 37 (23) | 4.73 (2.50-8.96) | <0.001 |
| Ambulatory treatment | 185 (74) | 132 (83) | 1.69 (1.02-2.80) | 0.040 |
| Previous use of ceftriaxone | 15 (6) | 22 (14) | 2.51 (1.26-4.99) | 0.009 |
| Previous use of ceftazidime | 1 (0.5) | 5 (3) | 8.05 (0.93-69.57) | 0.058 |
| Previous use of amoxycillin-clavulanic acid | 4 (2) | 12 (7) | 5.00 (1.58-15.79) | 0.006 |
| Previous use of ertapenem | 6 (2) | 15 (9) | 4.22 (1.60-11.12) | 0.004 |
| Previous use of levofloxacin | 5 (2) | 13 (8) | 4.35 (1.52-12.44) | 0.006 |
| Previous use of cephalosporins | 15 (6) | 29 (18) | 3.48 (1.80-6.73) | <0.001 |
| Previous use of penicillin | 10 (4) | 22 (14) | 3.84 (1.77-8.34) | 0.001 |
| Previous use of carbapenem | 8 (3) | 18 (11) | 3.85 (1.63-9.07) | 0.002 |
| Previous use of fluoroquinolones | 14 (5) | 25 (16) | 3.13 (1.57-6.23) | 0.001 |

UTI patients presenting at the Department of Emergency Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok over a one-year period. The proportion of patients with community-acquired ESBL *E.coli* UTI in the present study was lower than those reported from Western countries, which ranged from 77% to 79.5% (Calbo *et al*, 2006; Thaden *et al*, 2016). Studies showed that a history of antibiotics use (*viz*, beta-lactams, cefuroxime and fluoroquinolones) increases the risk of ESBL *E. coli* UTI from 5 to 21 times, depending on the type of drug (Rodríguez-Baño *et al*, 2004; Calbo *et al*, 2006; Yilmaz *et al*, 2008; Azap *et al*, 2010). In this study, cephalosporin and penicillin use increased the risk of ESBL *E. coli*-related infection by about 2-fold. These two antibiotics are commonly used in Thailand and have previously been reported to be associated with ESBL *E. coli* UTI in Spain (Rodríguez-Baño *et al*, 2004; Calbo *et al*, 2006). The mechanism was suggested as being a change in gastrointestinal microflora resulting in an increase in the proportion of ESBL *E. coli* in fecal samples (Valverde *et al*, 2004; Calbo *et al*, 2006).

Foley catheter use and previous UTI involving beta-lactamase *E. coli* were two other independent risk factors for ESBL

Table 4
Multivariate logistic regression analysis of factors associated with community-acquired extended spectrum beta-lactamase (ESBL) *E. coli* urinary tract infection (UTI).

| Factor | Non-ESBL *E. coli* ($N$ = 249) | ESBL *E. coli* ($N$ = 159) | OR (95%CI) | $p$-value |
|---|---|---|---|---|
| | No. of patients (%) | No. of patients (%) | | |
| On urinary catheter | 15 (6) | 32 (20) | 3.34 (1.69-6.56) | <0.001 |
| Previous UTI with beta-lactamase *E. coli* | 23 (9) | 30 (19) | 3.42 (1.75-6.70) | <0.001 |
| Previous use of cephalosporins | 15 (6) | 29 (18) | 2.18 (1.06-4.46) | 0.032 |
| Previous use of penicillin | 10 (4) | 22 (14) | 2.74 (1.19-6.32) | 0.016 |

*E. coli* UTI, similar to previous reports (Yilmaz *et al*, 2008; Azap *et al*, 2010). Other independent risk factors that have previously been reported include old age, diabetes and prostatic disease (Rodríguez-Baño *et al*, 2004; Azap *et al*, 2010). However, by application of multivariate logistic analysis, we were able to rule out these (and other) factors as constituting independent risk parameters.

In conclusion, the study shows that applying multivariate logistic analysis of retrospective factors associated with community-acquired ESBL *E. coli* UTI allowed identification of the independent risk factors of Thai patients attending a hospital emergency unit. Such information should be useful in the implementation of more targeted public health prevention and control programs, not only for Thailand but also for other regions of the world as the risk factors identified are of a universal character.

## ACKNOWLEDGEMENTS

The study was supported by The Thailand Research Fund (TRF; grant no. IRG 5780016); the Higher Education Research Promotion and National Research University Project of Thailand, Office of the Higher Education Commission, Thailand, through the Health Cluster (SHep-GMS); the Faculty of Medicine, Khon Kaen University (grant no. TR57201); and the TRF Senior Research Scholar Grant (grant no. RTA5880001). The authors thank Mr Dylan Southard, Research Affair, Faculty of Medicine, Khon Kaen University, for assistance in correcting the English of the manuscript.

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