RISK FACTORS AND CLINICAL OUTCOMES OF EXTENDED SPECTRUM BETA-LACTAMASE (ESBL)-PRODUCING *ESCHERICHIA COLI* SEPTICEMIA AT SRINAGARIND UNIVERSITY HOSPITAL, THAILAND

Siriluck Anunnatsiri[1], Patapong Towiwat[2] and Prajuab Chaimanee[3]

[1]Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University; [2]Department of Medicine, Faculty of Medicine, Khon Kaen University; [3]Clinical Microbiological Laboratory Unit, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand

Abstract. *Escherichia coli* producing extended spectrum beta-lactamase (ESBL) has emerged as a worldwide, public health problem. The aims of this study were to determine the incidence of ESBL-producing *E. coli* septicemia and evaluate the factors associated with the infection and the clinical outcomes. We reviewed 145 cases of *E. coli* septicemia among adult patients admitted to Srinagarind University Hospital in northeastern Thailand between 2005 and 2006. The incidence of ESBL-producing *E. coli* septicemia was 9.9 cases per 10,000 hospital admissions. The factors significantly associated with ESBL-producing *E. coli* septicemia were: 1) hospital acquisition [odds ratio (OR) 6.46; 95% confidence interval (CI) 2.01-20.79], 2) previous use of a fluoroquinolone (OR 19.14; 95%CI 5.82-62.96), and 3) use of a central venous catheter (OR, 8.59; 95%CI, 1.11-66.27). Seventy-two hours after receiving empiric treatment, a significantly greater proportion of patients with ESBL-producing *E. coli* septicemia had a worse clinical outcome than those with non-ESBL producing *E. coli* septicemia (p=0.01). The overall mortality rate was significantly higher among the ESBL-producing *E. coli* septicemia group than the non-ESBL producing *E. coli* septicemia group (29% *vs* 11.5%, respectively, p= 0.02). A high APACHE II score, ESBL-producing *E. coli* septicemia, primary septicemia, and having a non-urinary tract infecting as a source of septicemia were significantly independent factors related to mortality among patients with *E. coli* septicemia. ESBL-producing *E. coli* septicemia is an important cause of nosocomial infection and is related to higher mortality risk, especially among those with primary septicemia and secondary septicemia due to a non-urinary tract infection.

Keywords: septicemia, ESBL, *Escherichia coli*, Thailand

Correspondence: Dr Siriluck Anunnatsiri, Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Tel: 66 (0) 43 363664; Fax: 66 (0) 43 203772
E-mail: asiril@kku.ac.th

INTRODUCTION

Escherichia coli is a common cause of community-acquired and nosocomial bacteria infections. Extended spectrum beta-lactamase (ESBL)-producing *E. coli* infections first occurred in the nosocomial

setting then spread to community-acquired infection. It is now a major public health problem. ESBL-producing *E. coli* now accounts for 34.9 - 42.2% of *E. coli* infections in the Asia/Pacific region with India and China being the most affected (Hawser *et al*, 2009). In Thailand, studies conducted in 2003 and 2006 at university and provincial hospitals found ESBL-producing *E. coli* isolates in 13% and 38% of *E. coli* infections, respectively (Ingviya *et al*, 2003; Chayakulkeeree *et al*, 2005; Tharavichitkul *et al*, 2005; Waiwarawooth *et al*, 2006).

The epidemiology of ESBL-producing *E. coli* infection is changing, therefore monitoring its incidence is warranted. The important issues related to ESBL-producing *E. coli* are multiple antimicrobial resistance which leads to a delay in appropriate treatment, a higher mortality rate and the need to implement infection control to prevent further outbreaks. A knowledge of the risk factors related to septicemia caused by this organism is important for early detection and defining appropriate empirical treatment; however, few studies have focused on the factors related to ESBL-producing *E. coli* septicemia (Rodriguez-Bano *et al*, 2008, 2010; Wu *et al*, 2010).

The aims of the present study were to assess the incidence of ESBL-producing *E. coli* septicemia, determine the factors associated with contracting this type of infection and their clinical outcomes and determine the factors related to mortality among the patients with *E. coli* septicemia.

MATERIALS AND METHODS

A retrospective study was conducted among patients aged >15 years, admitted to Srinagarind Hospital, a 1,000-bed, tertiary care university hospital in northeastern Thailand. Study patients were identified through the database of the clinical microbiological laboratory of patients admitted to the hospital during 2005-2006 who had culture-confirmed *E. coli* septicemia. Patients with a second episode of *E. coli* or in patient with multiple organisms including *E. coli* causing septicemia were excluded.

Data obtained from the medical records were: demographics, potential risk factors for developing ESBL-producing *E. coli* septicemia, clinical management and risk factors for mortality, age, sex, type of infection, ward admitted to, comorbid diseases/conditions, previous antibiotic therapy (for at least 24 hours during the 3-months preceding septicemia), site of infection, drug susceptibility, prescribed antimicrobial agents, clinical outcome and length of hospitalization.

The severity of illness was estimated using the APACHE II score on the day of a positive blood culture or within 24 hours of a positive blood culture. The date included recent ICU stay, previous surgery, previous history of *E. coli* colonization, previous bacteremia due to other organisms, treatment with cytotoxic drugs or corticosteroids (≥20 mg/day for >5 days) within 30 days of septicemia, and invasive procedures performed from 48 hours to 7 days prior to documented septicemia were recorded.

Definitions

Empiric antimicrobial therapy was considered appropriate if the organism was susceptible *in vitro* to at least 1 of the drugs administered within 72 hours after documented septicemia. Appropriate antibiotic treatment during septicemia was defined as same as the appropriate empiric antimicrobial therapy but the drug(s) was (were) prescribed after 72 hours of sep-

ticemia and during septicemia. Clinical outcomes were assessed 72 hours after treatment: 1) a complete response (resolution of clinical sepsis), 2) a partial response (improvement in sepsis without complete resolution), and 3) failure (absence of improvement, worsening of sepsis).

Blood cultures were carried out using the BacTAlert automated culture system following the manufacturer's instructions. ESBL-producing *E. coli* isolates were identified by standard microbiological techniques using the double disk approximation test. Antimicrobial susceptibility testing was determined using the disk diffusion technique, in accordance with the Clinical and Laboratory Standards Institute criteria (NCCLS, 2000). Intermediate susceptibility to antibiotics was considered as having "resistance".

Statistical analysis

Data analyses were performed using SPSS, version 11.5 (SPSS, Chicago, IL). Categorical variables were compared using Fisher's exact or Pearson's chi-square tests where appropriate. The Student's *t*-test or Wilcoxon and Kruskal-Wallis tests were used to test for statistical significance of the continuous variables where appropriate. Univariate analysis was used to identify significant factors, the results being presented as odds ratios (OR) with 95% confidence intervals (95%CI). Multiple logistic regression analysis, using backward likelihood ratio selection, was used to assess the factors related to contracting ESBL-producing *E. coli* septicemia and factors related to mortality among patients with *E. coli* septicemia. A *p*-value of ≤0.05 was considered statistically significant.

RESULTS

During the 2-year study period, there were 324 episodes among 306 patients with positive blood cultures for *E. coli*; 43.1 cases per 10,000 hospital admissions. The incidence of ESBL-producing *E. coli* septicemia was 9.9 cases per 10,000 hospital admissions. The medical records of 206 cases (67.3%) were available for review. Of these, 61 cases were excluded from the study due to: mixed infection (25 cases) or being transferred to other hospitals (36 cases). Of the remaining 145 cases, 113 (78%) and 32 (22%) had non-ESBL- and ESBL-producing *E. coli*, respectively.

The demographic data are presented in Table 1. The mean age of the two patient groups (those with non-ESBL-producing and ESBL-producing *E. coli* septicemia) were not significantly different [55.9 (SD, 16.0) *vs* 55.3 (SD, 14.0) years]. There were no difference in sex distribution and underlying diseases between the groups. Eighty-eight percent of patients in each group had secondary septicemia; urinary tract infection (65 cases; 44.8%) was the most common source of septicemia, followed by intra-abdominal infection (55 cases; 37.9%). There were no significant differences in the proportions with urinary tract infection and intra-abdominal infection between the two groups.

On univariate analysis, the factors significantly associated with ESBL-producing *E. coli* septicemia were: 1) hospital-acquired infection, 2) non-medical patients, 3) prior ESBL-producing *E. coli* colonization, 4) prior antibiotic therapy, 5) recent surgery, 6) having received an intervention, such as nosogastric intubation, central venous catheterization or biliary drainage and 7) prolouged hospitalization (Table 1).

Prior receipt of any of the following four antimicrobial classes was significantly associated with ESBL-producing

Table 1
Demographic data and risk factors for ESBL-producing *E. coli* septicemia.

Variable	No. (%) of cases		*p*-value	OR (95%CI)
	Non-ESBL *E. coli* (*N*=113)	ESBL-*E. coli* (*N*=32)		
Mean age, years (±SD)	55.9 (16.0)	55.3 (14.0)	0.84	NS
Male	48 (42.5)	17 (53.1)	0.29	NS
Type of infection			<0.001	8.3 (3.37-20.47)
Hospital-acquired	30 (26.5)	24 (75)		
Community-acquired	83 (73.5)	8 (25)		
Admission ward		0.005		
Medicine	67 (59.3)	10 (31.3)		1
Surgery	37 (32.7)	14 (43.8)		2.54 (1.03-6.27)
Other	9 (8)	8 (25)		5.96 (1.87-19.02)
Underlying diseases	104 (92)	31 (96.9)	0.46	NS
Malignancy	46 (40.7)	17 (53.1)	0.21	NS
Received prednisolone or immunosuppressive drugs	23 (20.4)	9 (28.1)	0.35	NS
Diabetes mellitus	23 (20.4)	8 (25)	0.57	NS
Chronic liver disease	20 (17.7)	4 (12.5)	0.49	NS
Chronic kidney disease	13 (11.5)	7 (21.9)	0.15	NS
Heart disease	8 (7.1)	3 (9.4)	0.71	NS
Neutropenia	8 (7.1)	3 (9.4)	0.71	NS
Common bile duct stone	9 (8)	2 (6.3)	1.00	NS
Autoimmune disease	6 (5.3)	0 0.34	-	
Kidney transplant	2 (1.8)	1 (3.1)	0.53	NS
Prior ICU stay	3 (2.7)	3 (9.4)	0.12	NS
Prior ESBL-producing *E.coli* colonization	3 (2.7)	6 (18.8)	0.004	8.46 (1.98-36.08)
History of prior bacteremia	5 (4.4)	4 (12.5)	0.11	NS
History of prior antibiotic use	30 (26.8)	26 (81.3)	<0.001	11.84 (4.44-31.60)
3rd gen cephalosporin	16 (14.2)	19 (59.4)	<0.001	8.86 (3.67-21.40)
Beta-lactam/bata-lactamase inhibitor	10 (8.8)	8 (25)	0.03	3.43 (1.23-9.62)
Metronidazole	12 (10.6)	15 (46.9)	<0.001	7.43 (2.97-18.57)
Carbapenems	5 (4.4)	1 (3.1)	1.00	NS
Aminoglycosides	7 (6.2)	3 (9.4)	0.69	NS
Fluoroquinolone	10 (8.8)	17 (53.1)	<0.001	11.67 (4.51-30.20)
Penicillin group	5 (4.4)	8 (25)	0.001	7.2 (2.17-23.95)
Trimethoprim-sulfamethoxazole	4 (3.5)	2 (6.3)	0.61	NS
1st or 2nd gen cephalosporin	2 (1.8)	3 (9.4)	0.07	NS
Median (range) no. of previous antibiotics (*n*=56)	2.5 (1-6)	3 (1-7)	0.15	NS
No. of previous antibiotics (*n*=56)			0.21	NS
1-3	25 (83.3)	18 (69.2)		
≥4	5 (16.7)	8 (30.8)		
Median (range) duration of previous antibiotics used days (*n*=56)	15 (1-122)	19.5 (2-57)	0.71	NS

Table 1 (Continued).

Variable	No. (%) of cases		*p*-value	OR (95%CI)
	Non-ESBL *E. coli* (*N*=113)	ESBL-*E. coli* (*N*=32)		
Median (range) duration of hospitalization prior to having bacteremia, days	0 (0-82)	4 (0-66)	<0.001	1.03 (1.01-1.06)[a]
Intervention				
Foley catheter	14 (12.4)	7 (21.9)	0.25	NS
Nasogastric tube	4 (3.5)	7 (21.9)	0.002	7.63 (2.07-28.08)
Recent surgery	3 (2.7)	7 (21.9)	0.001	10.27 (2.48-42.50)
Percutaneous transhepatic biliary drainage	4 (3.5)	5 (15.6)	0.03	5.05 (1.27-20.07)
Central venous catheter	2 (1.8)	5 (15.6)	0.006	10.28 (1.89-55.86)
Radiation	3 (2.7)	3 (9.4)	0.12	NS
Gastrointestinal endoscopy	3 (2.7)	2 (6.3)	0.31	NS
Parenteral nutrition	0	4 (12.5)	0.002	-
On ventilator	1 (0.9)	2 (6.3)	0.12	NS
Peritoneal dialysis	2 (1.8)	0	1.00	-
Enterostomy	2 (1.8)	0	1.00	-
Type of bacteremia			1.00	NS
Primary	14 (12.4)	4 (12.5)		
Secondary	99 (87.6)	28 (87.5)		
Mean (SD) APACHE II score (*n*=137)[b]	16.25 (7.10)	16.73 (6.43)	0.74	NS

[a]Per 1-point increment; [b]8 missing data (6 with non-ESBL *E. coli* septicemia, 2 with ESBL-*E. coli* septicemia)

E. coli septicemia: third generation cephalosporin (OR 8.86; 95%CI 3.67-21.40), beta-lactam/beta-lactamase inhibitor (OR 3.43; 95%CI 1.23-9.62), metronidazole (OR 7.43; 95%CI 2.97-18.57), a fluoroquinolone (OR 11.67; 95%CI 4.51-30.20) or a penicillin group drug (OR 7.20; 95%CI 2.17-23.95). On multivariate analysis, three factors were independently associated with contracting ESBL-producing *E. coli* septicemia: hospital-acquired infection (OR 6.46; 95%CI 2.01-20.79), prior receipt of a fluoroquinolone (OR 19.14; 95%CI 5.82-62.96), and having central venous catheterization (OR 8.59; 95%CI 1.11-66.27).

The proportion of patients who received appropriate empiric antimicrobial therapy was significantly lower among patients with ESBL-producing *E. coli* septicemia (65.6% *vs* 98.2%, $p<0.001$) (Table 2). There were no differences between groups in the proportion of patients who received an appropriate antibiotic after pathogen identification. The median (range) duration from documented septicemia to receipt of appropriate antimicrobial therapy was significantly longer among patients with ESBL-producing *E. coli* septicemia [0.5 (0-6) *vs* 0 (0-4) days; $p<0.001$].

Survival at 72 hours after documented septicemia was evaluated in 143 cases because two cases were referred to another hospital during those 72 hours. There were no differences in mortality rate at 72 hours between the two groups, but the overall in-hospital mortality rate was significantly higher among patients with ESBL-producing *E. coli* septicemia (9 cases;

Table 2
Clinical outcome among patients with ESBL-producing *E. coli* septicemia.

Characteristic	No. (%) of cases		*p*-value
	Non-ESBL *E. coli* (*N*=113)	ESBL-*E. coli* (*N*=32)	
No. of patients receiving appropriate empirical antibiotic within 72 hours of septicemia	111 (98.2)	21 (65.6)	<0.001
No. of patients receiving appropriate antibiotics during the course of septicemia	111 (98.2)	30 (93.8)	0.21
Median (range) duration to receive appropriate antibiotic; days (*N*=141)	0 (0-4)	0.5 (0-6)	<0.001
No. of patients alive after 72 hours of empiric treatment (*N*=143)	105/112 (93.8)	29/31 (93.5)	1.00
Median (range) duration of hospitalization after septicemia; days (*N*=134)	8 (3-102)	13 (3-48)	0.01
Clinical outcome 72 hours after treatment (*N*=134)			0.01
Complete response	70/105 (66.7)	17/29 (58.6)	
Partial response	29/105 (27.6)	5/29 (17.2)	
Failure	6/105 (5.7)	7/29 (24.1)	
Overall in-hospital mortality	13 (11.5)	9 (29)	0.02

29% *vs* 13 cases; 11.5%, p=0.02). Of the 134 patients surviving 72 hours after treatment, a significantly greater proportion of patients with ESBL-producing *E. coli* septicemia (p=0.01) had a worse outcome (partial response or failure).

On univariate analysis, factors significantly related to mortality among patients with *E. coli* septicemia included a higher APACHE II score, having primary septicemia, having ESBL-producing *E. coli* septicemia, and having a non-urinary tract source of septicemia (Table 3). On multivariate analysis, four factors were independently related to mortality: 1) a high APACHE II score (OR 1.32; 95%CI 1.15-1.50), 2) having ESBL-producing *E. coli* septicemia (OR 7.76; 95%CI 1.84-32.72), 3) having primary septicemia (OR 5.96; 95%CI 1.19-29.77), and 4) having a non-urinary tract source of septicemia (OR 6.03; 95%CI 1.11-32.82).

DISCUSSION

ESBL-producing *E. coli* is a worldwide cause of serious nosocomial infections, having limited therapeutic options. This organism has emerged as an important cause of community-acquired infections, primarily urinary tract infection. Previous studies have shown independent factors related to ESBL-producing *E. coli* septicemia include: urinary catheterization, having an unknown bacteremic source, prolonged hospitalization, previous follow-up as an outpatient, having had an organ transplant, and having previous exposure to antibiotics (such as cephalosporins and fluoro-

Table 3
Factors associated with mortality among patients with *E. coli* septicemia.

Variable	Crude OR (95%CI)	Adjusted OR (95%CI)
Did not receive appropriate empirical antibiotics within 72 hours of septicemia onset	1.77 (0.45-7.01)	-
Did not receive appropriate antibiotics during the course of septicemia	1.89 (0.19-19.03)	-
APACHE II score	1.25 (1.13-1.39)	1.32 (1.15-1.50)
ESBL-producing *E. coli* septicemia	3.15 (1.20-8.28)	7.76 (1.84-32.72)
Primary septicemia	6.40 (2.17-18.90)	5.96 (1.19-29.77)
Secondary septicemia fromNon-UTI source	4.36 (1.39-13.62)	6.03 (1.11-32.82)
Delay in receiving appropriate antibiotics	1.14 (0.78-1.65)	-
Age	1.01 (0.98-1.04)	-

quinolones) (Rodriguez-Bano *et al*, 2008, 2010; Wu *et al*, 2010).

Except for previous exposure to fluoroquinolones, the present study found the different results for the independent factors associated with ESBL-producing *E. coli* septicemia were hospital-acquired infection, and central venous catheterization. Community-acquired infection was a negative predictive factor for ESBL-producing *E. coli* septicemia in the present study; however, up to 25% of patients with ESBL-producing *E. coli* septicemia had a community-acquired infection. This raises the spectra of emerging community-acquired ESBL-producing *E. coli*, but our study design did not enable us to confirm if the patients contracted a "true" community-acquired infection. Previous exposure to fluoroquinolones was strongly associated with acquiring ESBL-producing *E. coli* septicemia. The judicious use of this class of antimicrobial agents is strongly encouraged to reduce the risk for resistance.

ESBL-producing *E. coli* may result in higher the rates of treatment failure and death due to a delay in adequate antimicrobial therapy. Adequate, timely empirical antimicrobial therapy contributes to successful treatment of patients with septicemia. Similar to previous studies, the present study showed patients with ESBL-producing *E. coli* septicemia often miss receiving adequate empirical antimicrobial treatment; therefore, the time needed to receiving appropriate antibiotic therapy is longer (Melzer and Peterson, 2007; Gudiol *et al*, 2010). The impact of appropriate empirical antimicrobial therapy on clinical outcome is controversial. Some studies have shown a delay in appropriate antimicrobial therapy is not associated with higher mortality or shorten hospitalization (Kang *et al*, 2004; Thom *et al*, 2008) while other studies have found the opposite (Melzar and Peterson, 2007; Tumbarello *et al*, 2008). In the present study, a poor clinical outcome (inadequate response to treatment, prolonged hospitalization or higher in-hospital mortality) was more common among patients with ESBL-producing *E. coli* septicemia. ESBL-producing *E. coli* was an independent risk factor for mortality in these patients. This may be explained by

the higher probability these patients had inadequate initial antibiotic treatment and other factors influence mortality, such as a higher APACHE II score, an unknown source of bacteremia and a non-urinary tract infection source of septicemia. Assessment of factors related to contracting ESBL-producing *E. coli* should be performed among patients with suspected *E. coli* sepsis to enable timely, appropriate empiric antimicrobial therapy. This may improve clinical outcomes among these patients.

There were limitations to this study. Selection bias and incomplete data could not be avoided due to the retrospective study design. The small sample size may have influenced the non-significant findings in the study.

In conclusion, ESBL-producing *E. coli* was related to worse clinical outcomes among patients with *E. coli* septicemia, especially among very sick patients. A knowledge of the factors related to contracting this resistant pathogen as demonstrated in the present study may help physicians better target patients at higher risk, providing better prevention and treatment, to alleviate the problem of emerging resistant pathogens and improving clinical outcomes.

ACKNOWLEDGEMENTS

The authors thank the staff at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, for their care of the patients, the Hospital Medical Chart Registration and Clinical Microbiological Laboratory staff for their assistance and Mr Bryan Roderick Hamman and Mrs Janice Loewen Hamman for their assistance with the English-language presentation of the manuscript.

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