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นิพนธ์ต้นฉบับ Original Article

Community-onset Bloodstream Infection Caused by Extended Spectrum Beta-Lactamase Producing *Escherichia coli (E.coli)* at Tertiary-care Hospital in Thailand: Risk Factors and Clinical Outcome

ปัจจัยเสี่ยงและผลการรักษาการติดเชื้อในกระแสโลหิตจากชุมชนที่มีสาเหตุจากเชื้อ *Escherichia coli (E.coli)* ที่สร้างเอนไซม์ Extended Spectrum Beta-Lactamase (ESBL)

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ABSTRACT

Objective: To determine the local epidemiology, risk factors and outcome of community-onset bloodstream infection (COBSI) caused by extended spectrum beta-lactamase (ESBL) producing *E.coli*.

Material and methods: Retrospective study was conducted at Nakhonpathom Hospital during December 1, 2012 and June 30, 2013. Eligible patients were adults, aged ≥ 15 years, who had COBSI due to *E.coli.* Baseline characteristics, comorbid conditions, site and type of infection were collected. Risk factors for infection with ESBL-producing *E.coli* were identified. Predictive values for mortality were assessed.

Result: There were 102 and 71 (69.6%) patients were female. Thirty-two (31%) patients had ESBL and 70 (69%) had non-ESBL producing *E.coli* bacteremia. Sixty-nine (67.6%) and 33 (32.4%) patients were classified as having community associated and healthcare associated COBSI, respectively. Factors associated with ESBL-producing *E.coli* COBSI including prior antibiotics used within 3 months (OR 4.5, 95%CI 1.7-12.1, p = 0.002), previous cephalosporins exposure (OR 2.91, 95%CI 1.01-8.4, p = 0.04), previous fluoroquinolones exposure (OR 6.2, 95%CI 1.5-25.6, p = 0.01) and prior hospitalization within 3 months (OR 2.8, 95%CI 1.1-6.7, p = 0.02). The in-hospital mortality rate of ESBL and non-ESBL were 29% and 15.5%, respectively. Predictors associated with dead were severe sepsis (OR 23.3, 95% CI 6.7-81.9, p < 0.001) and inappropriate

empirical antimicrobial therapy (OR 3.3, 95%CI 1.2-9.2, p = 0.02). ESBL-producer did not influence outcome.

Conclusions: Infection caused by ESBL-producing *E.coli* is an emerging problem in community setting. Third-generation cephalosporins have been generally prescribed for community acquired sepsis. However, the high prevalence of ESBL producer in this study raises the question regarding the efficacy of them as an empirical therapy.

Keywords: community onset bloodstream infection, *E.coli*; extended spectrum beta-lactamase enzyme

บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความชุก ปัจจัยเสี่ยงต่อการสร้างเอนไซม์ extended spectrum beta-lactamase (ESBL) และปัจจัยเสี่ยงต่อการเสียชีวิตจากการติดเชื้อในกระแสโลหิตจากชุมชนที่มีสาเหตุจากเชื้อ *Escherichia coli (E.coli)*

วัสดุและวิธีการศึกษา: เป็นการศึกษาย้อนหลัง ในผู้ป่วยที่มีการติดเชื้อในกระแสโลหิตจากชุมชนที่มีสาเหตุจากเชื้อ *E.coli* ระหว่างวันที่ 1 ธันวาคม 2555 ถึง 30 มิถุนายน 2556 โดยศึกษาปัจจัยเสี่ยงต่อการติดเชื้อ *E.coli* ที่สร้างเอนไซม์ ESBL และปัจจัยเสี่ยงต่อการเสียชีวิต

ผลการศึกษา: ผู้ป่วยทั้งสิ้น 102 ราย เป็นหญิง 71 ราย (ร้อยละ 69.6) พบการติดเชื้อในกระแสโลหิตจากชุมชนที่มีสาเหตุจากเชื้อ *E.coli* ที่สร้างเอนไซม์ ESBL 32 ราย (ร้อยละ 31) และไม่สร้างเอนไซม์ ESBL 70 ราย (ร้อยละ 69) ปัจจัยเสี่ยงต่อการติดเชื้อที่สร้างเอนไซม์ ESBL ได้แก่ มีประวัติได้รับยาต้านจุลชีพมาก่อนภายใน 3 เดือน (OR 4.5, 95% CI 1.7-12.1, p = 0.002) มีประวัติได้รับยาต้านจุลชีพกลุ่ม cephalosporins (OR 2.91, 95% CI 1.01-8.4, p = 0.04) มีประวัติได้รับยาต้านจุลชีพกลุ่ม fluoroquinolones (OR 6.2, 95%CI 1.5-25.6, p = 0.01) และมีประวัติการนอนโรงพยาบาลมาก่อนภายใน 3 เดือน (OR 2.8, 95% CI 1.1-6.7, p = 0.02) เชื้อที่สร้างและไม่สร้างเอนไซม์ ESBL มีอัตราการเสียชีวิตเท่ากับร้อยละ 29 และ 15.5 ตามลำดับ ปัจจัยเสี่ยงต่อการเสียชีวิต ได้แก่ มีอาการและอาการแสดงของการติดเชื้ออย่างรุนแรง (OR 23.3, 95% CI 6.7-81.9, p < 0.001) และการได้รับยาต้านจุลชีพที่ไม่เหมาะสม (OR 3.3, 95% CI 1.2-9.2, p = 0.02) การสร้างเอนไซม์ ESBL ของเชื้อ *E.coli* ไม่มีผลต่ออัตราการเสียชีวิต

สรุป: การเลือกใช้ยาต้านจุลชีพเพื่อ empirical treatment ผู้ป่วยติดเชื้อในกระแสโลหิตจากชุมชน ควรพิจารณาถึงปัจจัยเสี่ยงต่อการติดเชื้อดื้อยา โดยเฉพาะเชื้อที่สร้างเอนไซม์ ESBL ซึ่งปัจจุบันมีแนวโน้มที่สูงขึ้น

คำสำคัญ: การติดเชื้อในกระแสโลหิตจากชุมชน เชื้อ *E.coli* เอนไซม์ extended spectrum beta-lactamase

Introduction

Escherichia coli (E.coli) is the most prominent cause of community-onset bloodstream infection (COBSI)[1-2]. Delay in initiation of appropriate antimicrobial therapy has been identified as an important determinant of outcomes[3]. Selection of such regimens is based on knowledge of local antibiogram. According

to the wide spread use of antibiotics, anti-microbial resistance particular extended spectrum beta-lactamase (ESBL) producing pathogens had emerged as a significant cause of community acquired infection[4-6]. Prevalence of ESBL producing *E.coli* among COBSI has been reported to be 3.6 to 14.3%[7-12]. There is little informations from Thailand, only 2 studies reported the prevalence of 8.8% and 11.8%.[1,13] The aim of the study was to determine the local epidemiology, risk factors and outcome of COBSI due to ESBL producing *E.coli.*

Material and methods

The retrospective study was carried out at Nakhonpathom Hospital, a 500-bed tertiary care hospital in central Thailand during December 1, 2012 and June 30, 2013. Eligible patients were adults, aged ≥ 15 years, who had COBSI due to *E.coli*. Patients were excluded if they had a second episode of *E.coli* bacteremia or had a blood culture positive for multiple organisms. Baseline data were extracted from the medical records including demographic data (age and gender), the presence of underlying diseases (diabetes mellitus, chronic kidney disease, chronic liver disease, pulmonary disease, HIV infection, hematologic malignancy and solid tumor), type of infection (healthcare-associated or community-acquired bacteremia), site of infection and the presence of severe sepsis. The comorbid conditions were documented: previous use of antibiotics (within 3 months), prior hospitalization (within 3 months), history of urinary tract infection (UTI), prior ESBL-producing *E.coli* colonization, the presence of an indwelling urinary catheter, a recent operation (within 3 months) and corticosteroids use (within 3 months). Clinical outcomes were assessed at hospital discharge.

Definitions

COBSI was defined when infection occurred within 48 hour of hospitalization and was further classified into healthcare-a ssociated bloodstream infection (HCABSI) and community-acquired bloodstream infection (CABSI). HCABSI was defined if any of the following criteria were presented: a history of a 48-hour hospital admission in the previous 90 days, hemodialysis, intravenous medication, residence in a nursing home or long-term care facility. Cases that did not fit criteria for HCABSI were identified as CABSI.

Severe sepsis was defined as sepsis with: (1) evidence of organ hypoperfusion; or (2) systolic blood pressure < 90 or < 30 mmHg less than baseline and requirement of vasopressor to maintain blood pressure. Appropriate antimicrobial therapy was defined if the initial antibiotics, which were administered within 24 hour after acquisition of blood culture samples was active in in vitro susceptibility testing.

Statistical analysis

All statistical analyses were performed

using SPSS software (version 16; SPSS, Inc., Chicago, IL, USA). Bivariate analyses were performed separately for each of the variables. The p-value were calculated by Fisher's exact test for categorical variables and by Student's t-test for continuous variables and p-values of < 0.05 was considered statistical significant.

Results

A total of 102 patients were enrolled, 69.6% were female. The elderly (age 65 and over) made up around 45% of patients. Thirty-two (31%) patients had ESBL and 70 (69%) had non-ESBL producing *E.coli* bacteremia. Sixty-nine (67.6%) patients were classified as having CABSI and the rate of ESBL producing E.coli was 23.2%, while 33 (32.4%) were classified as having HCABSI and ESBL producing was documented in 45.5%. Most of the patients (85.3%) had underlying diseases, including diabetes mellitus (51%), chronic kidney disease (14.7%), solid tumor (10.8%), chronic liver disease (8.8%) and pulmonary disease (3.9%). There were no differences among mean age, sex distribution and underlying diseases between ESBL and non-ESBL producer. Source of bacteremia was identified in 55.9% of cases. The most common were UTI (41.2%), followed by biliary tract infection (6.9%), spontaneous bacterial peritonitis (2%) and intra-abdominal infection (1%). Severe sepsis was documented in 27.4%. In addition, source of bacteremia and severity of illness were not significant difference between the two groups. Twenty-nine patients (28.4%) did not receive appropriate antimibrobial therapy, the proportion was significant higher among patients with ESBL-producer (78.1% vs 5.7%, $p < 0.001$).

Several factors were associated with ESBL-producing *E.coli* COBSI, these included a prior receipt of antibiotics (OR 4.5, 95% CI 1.7-12.1, $p = 0.002$), previous use of cephalosporins (OR 2.91, 95% CI 1.01-8.4, $p = 0.04$), previous use of fluoroquinolones (OR 6.2, 95% CI 1.5-25.6, $p = 0.01$) and history of hospitalization (OR 2.8, 95% CI 1.1-6.7, $p = 0.02$). History of UTI, previous colonization with ESBL-producing *E.coli*, urinary catheterization, recent operation and corticosteroid usage were not shown to be risk factors for ESBL-producing *E.coli* COBSI.

The in-hospital mortality rate of ESBL and non-ESBL were 29% and 15.5%, respectively. Predictors associated with dead were severe sepsis (OR 23.3, 95% CI 6.7-81.9, $p < 0.001$), and inappropriate empirical antimicrobial therapy (OR 3.3, 95% CI 1.2-9.2, $p = 0.02$).

Discussion

The prevalence of COBSI due to ESBL-producing *E.coli* in our study was 31%, which was much higher than those observed in previous reports [7-13]. This could be explained by lack of antimicrobial stewardship, indiscriminate antibiotics usage and under supported infection control practices in the country. However, blood culture may not routinely be undertaken in all

Table 1 Demographic data, risk factors and outcome for COBSI due to ESBL-producing *E.coli* [a]16 missing data (2 with ESBL *E.coli* bacteremia, 14 with non-ESBL *E.coli* bacteremia), [b]25 missing data (4 with ESBL *E.coli* bacteremia, 21 with non-ESBL *E.coli* bacteremia)

Variable	No. (%) of patients		*P*-value	OR (95% CI)
	ESBL *E.coli* (n = 32)	Non-ESBL *E.coli* (n = 70)		
Mean age, years (± S.D.)	64.0 (15.0)	61.5 (16.8)	0.47	-
Elderly (age ≥ 65 yr)	15 (46.9)	31 (44.3)	0.81	NS
Female	19 (59.4)	52 (74.3)	0.13	NS
Type of infection			0.03	0.4 (0.2-0.9)
Community-acquired	17 (53.1)	52 (74.3)		
Healthcare-associated	15 (46.9)	18 (25.7)		
Underlying diseases	29 (90.6)	58 (82.9)	0.38	NS
Diabetes mellitus	14 (43.8)	38 (54.3)	0.32	NS
Chronic kidney disease	5 (15.6)	10 (14.3)	1.00	NS
Solid tumor	4 (12.5)	7 (10.0)	0.74	NS
Chronic liver disease	3 (9.4)	6 (8.6)	0.89	NS
Pulmonary disease	1 (3.1)	3 (4.3)	1.00	NS
Hematologic malignancy	1 (3.1)	0	0.31	NS
HIV infection	0	1 (1.4)	1.00	NS
Comorbid condition (n = 86)[a]	21 (70.0)	25 (44.6)	0.03	2.9 (1.1-7.4)
Prior antibiotics use (n = 77)[b]	18 (64.3)	14 (28.6)	0.002	4.5 (1.7-12.1)
Cephalosporins	11 (40.7)	9 (19.1)	0.04	2.9 (1.01-8.4)
Fluoroquinolones	8 (29.6)	3 (6.4)	0.01	6.2 (1.5-25.6)
Others	7 (25.9)	4 (8.5)	0.09	NS
Prior hospitalization	15 (46.9)	17 (24.3)	0.02	2.8 (1.1-6.7)
Previous urinary tract infection	5 (15.6)	7 (10.0)	0.51	NS
Prior ESBL-producing *E.coli* colonization	6 (18.8)	5 (7.1)	0.10	NS
Indwelling urinary catheter	4 (12.5)	3 (4.3)	0.20	NS
Recent operation	2 (6.2)	5 (7.1)	1.00	NS
Corticosteroid use	1 (3.1)	2 (2.9)	1.00	NS
Source of bacteremia, known	15 (46.9)	40 (57.1)	0.33	NS
Urinary tract infection	11 (34.4)	31 (44.3)	0.35	NS
Biliary tract infection	4 (12.5)	3 (4.3)	0.20	NS
Spontaneous bacterial peritonitis	0	2 (2.9)	1.00	NS
Intra-abdominal infection	1 (3.1)	0	0.31	NS
Others	1 (3.1)	4 (5.7)	1.00	NS
Severe sepsis	10 (31.2)	18 (25.7)	0.56	NS
Inappropriate empirical antibiotics	25 (78.1)	4 (5.7)	< 0.001	58.9 (15.9-218.8)
In-hospital mortality	9 (28.1)	11 (15.7)	0.14	NS

Table 2 Factors associated with in-hospital mortality for COBSI due to ESBL-producing *E.coli*

	No. (%) of patients		*P*-value	OR (95% CI)
	Dead (n = 20)	Survivors (n = 82)		
ESBL *E.coli*	9 (45.0)	23 (28.0)	0.14	NS
Severe sepsis	16 (80.0)	12 (14.6)	< 0.001	23.3 (6.7-81.9)
Inappropriate empirical antibiotics	10 (50.0)	19 (23.2)	0.02	3.3 (1.2-9.2)
Urinary tract infection	7 (35.0)	35 (42.7)	0.53	NS
Diabetes mellitus	8 (40.0)	44 (53.7)	0.27	NS
Elderly (age ≥ 65 yr)	11 (55.0)	35 (42.7)	0.32	NS

patients especially those who were not presented with severe sepsis. Moreover, patients are able to self-medicate over-the-counter antimicrobial agents which may be active against *E.coli*. Thus this may not provide the true prevalence of ESBL producer.

Several studies demonstrated significant factors for acquiring community-associated ESBL infection include: previous hospitalization, prior antibiotics use, recent exposure to cephalosporins or fluoroquinolones, urinary catheterization, certain underlying disease (liver disease, DM), old age (age ≥ 65 years), female sex, recurrent UTI, previous ESBL-producing *E.coli* colonization and central venous catherization[7-10,14-16]. However, of all the risk factors found, only antibiotics exposure (particular cephalosporins and fluoroquino lones) and prior hospitalization were shown to be factors related to ESBL infection in this study.

Previous studies have reported mortality rates among COBSI caused by *E.coli* of 7-29%[7,9-10,17]. Various factors have been found to be responsible for higher patients mortality, these include malignancy, liver disease, severity of illness and inadequate empirical treatment[8,17]. Several studies did not demonstrate the association between ESBL-producer and outcome[7-10]. In this study, the mortality rate was 19.6% and there was no difference between ESBL and non-ESBL. Severe sepsis and inappropriate antibiotics treatment were the only 2 factors associated with dead in this study.

The study is limited by small sample size. Furthermore, because of the retrospective design of the study, there were some missing data on prior history and type of antibiotics

exposure. Notwithstanding these limitations, the findings were shown to be significant risk factors for ESBL-producing *E.coli* bacteremia.

Conclusion

Infection caused by ESBL-producing *E.coli* is an emerging problem in community setting. This data should help to improve public health awareness of high prevalence of antimicrobial resistance. Further studies are need to identify local epidemiology and risk factors for infection with ESBL producers. Third-generation cephalosporins such as ceftriaxone have been widely prescribed in several healthcare institutes as an empirical therapy for septic patients in a community setting, nevertheless the high prevalence of ESBL producer in this study raises the question regarding the efficacy of these agents as an empirical therapy.

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