Intra-Abdominal Infections: Prevalence and Risk Factors of ESBLs Infections

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Background: *Extended-Spectrum Beta-Lactamases (ESBLs)-producing bacteria are increasing challenge in the treatment of both community acquired and nosocomial intra-abdominal infections (IAIs). Investigating the characteristics of patients with the IAIs caused by ESBL-producing bacteria and assessing the risk factors of ESBLs infection will lead to appropriate therapeutic management.*

Objective: *To determine prevalence of ESBL-producing bacteria in IAIs in Phramongkutklao Hospital and identify risk factor of the ESBL-infections.*

Material and Method: *We performed a retrospective cross sectional study of patients admitted in Phramongkutklao Hospital between January 1 and December 30, 2012 to determine the prevalence and risk factors acquiring ESBL-producing bacteria in IAIs and the outcomes of these infections.*

Results: *Sixty-one patients were studied, of whom 45 (73.8%) had community-acquired and 16 (26.2%) had nosocomial IAIs. ESBL-producing bacteria were positive in 18 patients, 7 (15.6%) in community acquired and 11 (68.8%) nosocomial infection. The common gram negative bacilli were Escherichia coli, Klebsiella pneumoniae. Univariate analysis showed three factors including nosocomial infection, prior admission within one month, and prior use of antibiotics, in particular, cephalosporin, and beta-lactam/beta-lactamase inhibitor (BLBI), to be associated with ESBL-producing bacterial infections. In the multivariate analysis, nosocomial infection (odds ratio [OR], 5.26; 95% confidence interval [CI], (1.07-25.88); p = 0.041) was independent factor that related to the ESBL-infection in IAIs.*

Conclusion: *Nosocomial infection was found as an independent factor significantly associated with ESBL-infection in IAIs. Other critical issues remain debatable and more controversial are due to the limited number of the study's patients.*

Keywords: *Intra-abdominal infections, Extended-spectrum beta-lactamases, Nosocomial, E. coli*

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During the past two decades, worldwide incidence of emerging resistant bacteria was significantly increasing, among these Extended-Spectrum Beta-Lactamases (ESBLs)-producing Enterobacteriaceae, in particular: *Escherichia coli* and *Klebsiella pneumoniae* were recognized as a significant group of the resistant pathogens[1]. Further, ESBL-producing organisms have been frequently reported to be resistant to multiple antimicrobial agents causing limitation of therapeutic options for the infections, in which, only carbapenems are recommended for the treatment option of the serious bacterial infections[2]. More than half of the patients identified as ESBL-producing bacterial infections have been diagnosed of urinary tract infections (UTIs) and intra-abdominal infections (IAIs)[3]. However, there is limited publication on epidemiology of ESBL-producing bacterial infections, in particular, the clinical and microbiological epidemiology of ESBL-producing bacterial infections in IAIs.

In addition to the documentation of the pathogenic significance and incidence of ESBL-producing bacterial infections, it is also necessary to combine clinical data on risk factors of ESBL-producing bacterial infections. The important of identifying the co-operative data is for the development of effective treatment strategies for the ESBL-infections. Thus, the present study was performed to evaluate the clinical features, epidemiology, and to identify risk factors for the ESBL-producing bacterial infections. This knowledge is essential for selection of an appropriate empiric antimicrobial therapy for the infections.

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Material and Method

Study design and population

A retrospective study was performed to determine prevalence and to evaluate risk factors associated with ESBL-producing bacterial infections.

The medical records of individuals diagnosed with IAIs performing intra-operative abdominal fluid and/or tissue culture between January and December 2012 were reviewed. The sixty-one samples were collected from patients in Phramongkutklao Hospital, a tertiary care university hospital in Bangkok, Thailand. Patients were recruited in the present study if their cultures were drawn in the operating theatre.

Patient who had nosocomial infection was defined as a person whose infection acquired during hospital care, which was not presented or incubating at admission, or infections occurring more than 48 hours after admission[4].

Demographic data collected including age, gender, underlying disease, site of infection. The presence of the following conditions were documented; prior admission within one and three months, and prior usage of antibiotics. Results of cultures and treatments were also recorded. The present study was approved by the Institutional Review Board of Phramongkutklao Hospital, Bangkok, Thailand.

Statistical analysis

Student's t-test was used to compare continuous variables, and Chi-square test or Fisher's exact test was used to compare categorical variables. A stepwise conditional logistic regression analysis was used to control the effects of confounding variables and to identify the independent risk factors of infections. All risk factors with a *p*-value of <0.1 at the bivariate level were included in the multivariate logistic model for predicting ESBL-producing bacterial infections. All variables for which *p*-value was <0.05 in the multivariate analysis were retained in the final model. Odds ratios (ORs) and their 95% confidential intervals (CIs) were calculated. All *p*-values were two tailed, and a *p*-value of <0.05 was considered statistically significant.

Results

The demographic data and patient characteristics were summarized in Table 1. The mean age (SD) was 62.2 (19.5) years and majority of the patients (59%) were male. Of the 61 patients, 45 patients (73.8%) were classified as community acquired. The most common underlying diseases were hypertension (n = 35; 57.4%), followed by diabetes mellitus (n = 19; 31.1%) and chronic kidney disease (n = 6; 9.8%). From 61 patients, the abdominal fluid cultures were negative in 24 (39.3%). The two most common organisms found were *E. coli* and *K. pneumoniae*, among these 19 (31.1%) were ESBL-producer (Table 2).

All patients were analyzed the risks factors associated with ESBL-producing bacterial infections. The analysis showed nosocomial infection, prior admission within one month, and prior usage of

Table 1. Demographic data and patient characteristics (total n = 61)

Characteristic	n (%)
Gender	
Male	36 (59.0)
Female	25 (41.0)
Age (years)*	62.2 (19.5) (14-97)
Type of intra-abdominal infection (IAI)	
Community acquired	45 (73.8)
Nosocomial	16 (26.2)
Underlying disease	
Type II diabetes	
No	42 (68.9)
Yes	19 (31.1)
Hypertension	
No	26 (42.6)
Yes	35 (57.4)
Chronic kidney disease (CKD)	
No	55 (90.2)
Yes	6 (9.8)
Autoimmune	
No	59 (96.7)
Yes	2 (3.3)
Cerebro-vascular accident (CVA)	
No	56 (91.8)
Yes	5 (8.2)
Bed-ridden	
No	58 (95.1)
Yes	3 (4.9)

* Mean (SD) (min-max)

Table 2. Prevalence of extended-spectrum beta-lactamases (ESBL) from intra-abdominal infections

Organism	ESBL		Total n (%)
	Negative n (%)	Positive n (%)	
Escherichia coli	11 (39.3)	17 (60.7)	28 (42.4)
Klebsiella pneumoniae	5 (71.4)	2 (28.6)	7 (10.6)
Acinetobacter baumannii	1 (50.0)	1 (50.0)	2 (3.0)
Enterococcus faecium	2 (66.7)	1 (33.3)	3 (4.5)
Candida albicans	1 (100)	-	1 (1.5)
Streptococcus viridian	1 (100)	-	1 (1.5)
No growth	24 (100)	-	24 (36.4)
Total	45 (68.2)	21 (31.8)	66 (100)

cephalosporin and Beta-lactam Beta-lactamase inhibitor (BLBI) antibiotics were associated with ESBL-producing bacterial infections. The result of treatment was poor in ESBL-producer group (Table 3). However, in multivariate models, nosocomial infection (OR, 5.26; 95% CI, 1.07 to 25.88; $p = 0.041$) was the only independent factor found to be associated with ESBL-producing bacterial infections (Table 4).

Table 3. Clinical features and risk factors associated with ESBL-producing bacteria in IAIs

Clinical feature/risk factor	ESBL organisms		*p*-value
	Negative (43 patients)	Positive (18 patients)	
Age**	63 (17-89)	68 (14-97)	0.652‡
Gender			0.354*
Male	27 (75.0)	9 (25.0)	
Female	16 (64.0)	9 (36.0)	
Type II diabetes			0.114*
No	27 (64.3)	15 (35.7)	
Yes	16 (84.2)	3 (15.8)	
Hypertension			0.852*
No	18 (69.2)	8 (30.8)	
Yes	25 (71.4)	10 (28.6)	
Chronic kidney disease (CKD)			0.348†
No	40 (72.7)	15 (27.3)	
Yes	3 (50.0)	3 (50.0)	
Autoimmune			0.507†
No	42 (71.2)	17 (28.8)	
Yes	1 (50.0)	1 (50.0)	
Cerebro-vascular accident (CVA)			1.000†
No	39 (69.6)	17 (30.4)	
Yes	4 (80.0)	1 (20.0)	
Bed-ridden			0.205†
No	42 (72.4)	16 (27.6)	
Yes	1 (33.3)	2 (66.7)	
Type of IAI			<0.001†
Community	38 (84.4)	7 (15.6)	
Nosocomial	5 (31.3)	11 (68.8)	
Prior admission within 1 month			<0.001†
No	39 (83.0)	8 (17.0)	
Yes	4 (28.6)	10 (71.4)	
Prior admission within 3 months			0.084†
No	43 (72.9)	16 (27.1)	
Yes	-	2 (100.0)	
Prior use cephalosporin			0.018†
No	37 (78.7)	10 (21.3)	
Yes	6 (42.9)	8 (57.1)	
Prior use fluoroquinolone			-
No	43 (70.5)	18 (29.5)	
Yes	-	-	
Prior use beta-lactam beta-lactamase inhibitor (BLBI)			0.002†
No	41 (78.8)	11 (21.2)	
Yes	2 (22.2)	7 (77.8)	
Result of treatment			0.030†
Not cure	5 (41.7)	7 (58.3)	
Cure	38 (77.6)	11 (22.4)	

* Chi-square test, † Fisher's exact test, ‡ Mann-Whitney U test
** Median (min-max)

Table 4. Predisposing factors of ESBL-producing bacterial infections in IAIs

	ESBL organisms		Crude odds ratio (95%CI)	Adjusted odds ratio (95%CI)	*p*-value
	Negative (43 patients)	Positive (18 patients)			
Type of IAI					0.041
Community	38 (84.4)	7 (15.6)	1	1	
Nosocomial	5 (31.3)	11 (68.8)	11.94 (3.16-45.13)	5.26 (1.07-25.88)	
Prior admission within 1 month					0.072
No	39 (83.0)	8 (17.0)	1	1	
Yes	4 (28.6)	10 (71.4)	12.19 (3.05-48.77)	4.64 (0.87-24.71)	

Multiple logistic regressions: backward (Wald)
Adjusted by community & nosocomial, prior admission within 1 month, prior use cephalosporin, prior use BLBI and result of treatment

Discussion

Intra-abdominal infection (IAI) is classified into two groups: community-acquired IAI and nosocomial IAI, which are different in microbiology and treatment strategies. Community-acquired IAI is normally caused by non-resistant community-based pathogen, for example: *E. coli*, *K. pneumoniae*, and *Bacteroides fragillis*. On the other hand, nosocomial IAI is caused by resistant hospital-based pathogen including ESBL-producing *E. coli* or *K. pneumoniae*, *Pseudomonas aeruginosa*, and enterococci[5,6]. The management of IAI includes initial resuscitation, investigation, appropriate empiric antibiotic treatment, and adequate source control. Due to the dissimilarity in nature of the IAI pathogens, appropriate antibiotics for IAI were studied leading to the difference in antibiotic treatment. A recent publication was recommended a guideline for empiric antibiotic treatment for the groups of IAI[7,8]. Appropriate antibiotic therapy is considered to be affected factor for the outcome of IAI management.

In 1983, the first ESBL-producing bacteria was discovered and reported in *E. coli* and *Klebsiella* spp. By Knothe et al[9], and subsequently has been reported worldwide. Normally, Beta-lactamase enzymes were produced by both Gram-positive and Gram-negative bacterias to inhibit Beta-lactam antibiotics, e.g., penicillins and cephalosporins, but cannot inhibit the activity of third generation cephalosporin antibiotics, which was initially named as Extended-Spectrum Beta-Lactam antibiotics. However, these new type of Beta-lactamase enzymes can inhibit the activity of the third generation cephalosporin antibiotics, then this type of Beta-lactamase enzymes called "Extended-Spectrum Beta-Lactamases (ESBLs)"[10]. These enzymes commonly present in Gram-negative bacteria of the family Enterobacteriaceae, in particular, *E. coli*, and *Klebsiella* spp.[11].

The overall incidence of ESBL-producing bacteria in Thailand was reported approximately 35 to 40% and 40 to 45% for *E. coli* and *Klebsiella* spp., respectively[12]. The further study showed minimal incidence of ESBL-producing bacteria in the community-acquired patients; however, the study reported risk factors for ESBL-producing bacterial infections including patients frequently hospitalized by any causes, patients with recurrent urinary tract infections treated with the third generation cephalosporin or fluoroquinolone antibiotics[13,14]. These risks should be considered by clinicians since the third generation cephalosporin and fluoroquinolone antibiotics are ineffective for treatment in these groups of patients[15]. Up to date, recommended antibiotic for treatment of serious ESBL-producing bacterial infections is carbapenems, e.g., ertapenem, imipenem, meropenem, and doripenem, in particular, patients with severe sepsis[16]. The adequacy of the initial antibiotic therapy for the serious ESBL-infection was associated with mortality[17].

The present study showed that ESBL-producing *E. coli* was predominant organism of both community and nosocomial IAIs. Recently, several studies attempted to identify risk factors for ESBL-producing bacterial infections, in which, patients with history of prior usage of antibiotics found to be associated with ESBL-producing infections, however, focused mainly on urinary tract infections[18]. The present study provided an analysis of the risk factors of IAIs caused by ESBL-producing bacteria. Nosocomial infections, prior admission, prior use of cephalosporin, and BLBI antibiotics were found to be associated with ESBL-producing infections, moreover, the only independent risk factor

associated with the infections was nosocomial setting of the patients.

Community onset of the ESBL-producing bacterial infections in the present study accounted for 15.6%, which was more common than previous reported. However, the incidence of ESBL-producing bacterial infections in IAIs is probably underestimated, since cultured samples from patients with community-acquired IAIs are not routinely done. The finding from the present study also suggests that ESBL-producers have already begun to disseminate throughout the community. Nevertheless, determining the exact prevalence of these organisms would require a population-based study. Furthermore, the present study identified risk factors and outcomes, which showed association of several factors in univariate analysis but did not prove feasible in multivariate analysis because of the high number of patients with community onset infections.

The present study had several limitations. First, clinical data were retrospectively collected through electronic medical records and chart review, thus unknown risk factors may be unequally distributed in the study group. In addition, this study was observational in nature, which might be resulting in possibility of limitations that preclude accurate comparisons. Second, although this study was performed at a large tertiary care hospital, a relatively small number of patients were included, resulting in limited statistical power, which may have created instability in the multivariable logistic regression model. Finally, the present study was conducted mainly at large referral centers, thus many of the patients had serious underlying illnesses, and our findings might not be generalizable to other institutions, particularly community hospitals.

In conclusion, IAIs caused by multidrug-resistant bacteria, especially ESBL-producing Enterobacteriaceae, raised key therapeutic problems. This study confirmed that ESBL-producing *E. coli* strains were a notable cause of IAIs in predisposed patients. Nosocomial types of IAIs were significant factor associated with the ESBL-producing *E. coli* infections. The widespread and rapid dissemination of ESBL-producing *E. coli* seems to be an emerging issue worldwide, and ESBL-producing *E. coli* is a pathogen that is increasingly found in the community and that may drive significant changes in the empirical use of antibiotics for certain infections. Further clinical studies are needed to guide clinicians in the management of community onset infections caused by *E. coli*.

What is already known on this topic?

Currently, guidelines of antibiotic therapy for IAI were published in both U.S.A. and Europe, the recommendations were based on clinical data from their region.

Incidence of ESBL-infections in Asia was reported; however, publication of risk factors for the ESBL-infection in IAIs was limited.

What this study adds?

This report provides prevalence of ESBL-infection in patients documented of IAIs, accompanying with risk factors of the infections. These would be suggested the recommendation of the antibiotic therapy for this group of patients in the region.

Potential conflicts of interest

None.

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การศึกษาความชุกและปัจจัยเสี่ยงต่อการติดเชื้อดื้อยาปฏิชีวนะชนิด ESBL ในผู้ป่วยที่มีภาวะติดเชื้อทางช่องท้องในโรงพยาบาลพระมงกุฎเกล้า

ภิเษก บุญธรรม, รัฐพล สุนทรรักษ์

ภูมิหลัง: ปัจจุบันการติดเชื้อดื้อยาปฏิชีวนะชนิด ESBL สามารถพบได้มากขึ้นจนเป็นปัญหาต่อการรักษาในแผนกศัลยกรรม โดยเฉพาะอย่างยิ่งผู้ป่วยภาวะติดเชื้อทางช่องท้องมักพบในเชื้อกลุ่ม Enterobacteriaceae อาทิ E. coli, Klebsiella spp. ในอดีตการติดเชื้อกลุ่มนี้มักพบเฉพาะในผู้ป่วยที่เข้ารับการรักษาในโรงพยาบาลเท่านั้น อย่างไรก็ตามผู้ป่วยภาวะติดเชื้อทางช่องท้องจากชุมชนมีอุบัติการณ์การติดเชื้อดื้อยาปฏิชีวนะในกลุ่มนี้เพิ่มขึ้น ซึ่งการศึกษาที่ผ่านมายังไม่มีข้อมูลการติดเชื้อดื้อยาปฏิชีวนะชนิดนี้มากนักในผู้ป่วยภาวะติดเชื้อทางช่องท้องที่มาจากชุมชน

วัตถุประสงค์: การศึกษานี้ต้องการหาความชุกของการติดเชื้อดื้อยากลุ่มนี้ ในผู้ป่วยภาวะติดเชื้อช่องท้องทั้งจากชุมชนและผู้ป่วยที่รักษาตัวในโรงพยาบาล นอกจากนี้การศึกษานี้ยังต้องการศึกษาถึงปัจจัยเสี่ยงต่อการติดเชื้อดื้อยาชนิดนี้ในผู้ป่วยภาวะติดเชื้อทางช่องท้อง ทั้งสองกลุ่ม ซึ่งผลการศึกษานี้จะมีประโยชน์ในการตัดสินใจเลือกใช้ ยาปฏิชีวนะสำหรับการรักษาผู้ป่วยที่มีความเสี่ยงต่อการติดเชื้อดื้อยาชนิดนี้

วัสดุและวิธีการ: ใช้วิธีการเก็บข้อมูลจากแผนกศัลยกรรมโรงพยาบาลพระมงกุฎเกล้า เริ่มตั้งแต่ วันที่ 1 มกราคม พ.ศ. 2555 ถึง 31 ธันวาคม พ.ศ. 2555 รวมระยะเวลา 1 ปี โดยมีการเก็บข้อมูลผู้ป่วยทั่วไปในผู้ป่วยที่มีภาวะติดเชื้อทางช่องท้อง ความชุกของการติดเชื้อ ESBL ในประชากรที่ต้องการศึกษา การใช้ยาปฏิชีวนะก่อนหน้าการศึกษาครั้งนี้ โดยผู้ป่วยที่เข้าร่วมการศึกษาต้องมีผลการเพาะเชื้อทั้งจากเนื้อเยื่อจากการผ่าตัดทางช่องท้องหรือจากเลือดที่บ่งชี้ว่าการติดเชื้อในกลุ่มนี้จริง

ผลการศึกษา: ในการศึกษานี้ผู้ป่วยที่มีภาวะติดเชื้อทางช่องท้องเข้าร่วมการศึกษาทั้งสิ้น 61 ราย โดยพบว่าผู้ป่วยส่วนใหญ่เป็นผู้ป่วยซึ่งมาจากชุมชน ร้อยละ 73.8 และพบผู้ป่วยที่เป็นการติดเชื้อในโรงพยาบาล ร้อยละ 26.2 การติดเชื้อดื้อยาปฏิชีวนะชนิด ESBL พบในผู้ป่วยที่มาจากชุมชนร้อยละ 15.6 ซึ่งต่างจากผู้ป่วยที่ติดเชื้อในโรงพยาบาลซึ่งพบการติดเชื้อดื้อยาปฏิชีวนะชนิด ESBL ถึงร้อยละ 68.8 เชื้อที่พบเป็นเชื้อกลุ่ม Enterobacteriaceae ทั้ง E. coli และ Klebsiella pneumonia จากการคำนวณทางสถิติปัจจัยที่ส่งผลต่อการติดเชื้อดื้อยาปฏิชีวนะชนิด ESBL ในผู้ป่วยภาวะติดเชื้อทางช่องท้องนั้นพบว่า การใช้ยาปฏิชีวนะก่อนการเข้ารับการรักษาตัวในครั้งนี้ อาทิ ยาในกลุ่ม cephalosporin และ ยากลุ่ม BLBI มีผลต่อการติดเชื้อดื้อยาปฏิชีวนะกลุ่มนี้ นอกจากนี้การเข้ารักษาตัวในโรงพยาบาลภายใน 1 เดือน ก่อนหน้าการติดเชื้อครั้งนี้ และภาวะการติดเชื้อในโรงพยาบาลพบว่าเป็นปัจจัยเสี่ยงต่อการติดเชื้อดื้อยาปฏิชีวนะชนิดนี้เช่นกัน อย่างไรก็ตามเมื่อนำปัจจัยเสี่ยงทั้งหมดมาคำนวณทางสถิติชนิด multivariate พบว่าภาวะการติดเชื้อในโรงพยาบาลเป็นเพียงปัจจัยเดียวที่มีผลต่อการติดเชื้อดื้อยาปฏิชีวนะชนิด ESBL อย่างมีนัยสำคัญทางสถิติ

สรุป: ภาวะติดเชื้อทางช่องท้องเป็นปัญหาที่พบบ่อยในทางศัลยกรรม ดังนั้นการให้การรักษาที่ถูกต้องนอกเหนือจากการผ่าตัดที่ถูกต้องแล้วการให้ยาปฏิชีวนะที่เหมาะสมจะทำให้อัตราการรอดชีวิตของผู้ป่วยเพิ่มขึ้น การศึกษานี้นอกจากจะเป็นการชี้ให้เห็นถึงปัจจัยเสี่ยงของการติดเชื้อดื้อยาปฏิชีวนะชนิด ESBL แล้ว ยังแสดงให้เห็นว่าการติดเชื้อดื้อยาชนิดนี้ได้แพร่กระจายเข้าสู่แหล่งชุมชนแล้ว ถึงแม้ว่าจำนวนประชากรที่พบยังไม่มากถึงขนาดที่มีความสำคัญทางสถิติแต่คาดว่าในอนาคตเชื้อดื้อยาปฏิชีวนะชนิดนี้อาจพบเพิ่มขึ้นในผู้ป่วยที่มาจากชุมชนได้