Outcomes and Associated Factors of Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae Urinary Tract Infection among Patients with Long-Term Urinary Catheterization

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Objective: To study the clinical outcomes, economic burden, and associated factors in patients with long-term urinary catheterization who develop extended-spectrum beta-lactamase producing (ESBL) Enterobacteriaceae catheter associated urinary tract infection (CAUTI).

Materials and Methods: The retrospective cohort study was conducted in the long-term urinary catheterization in Songklanagarind Hospital between January 2010 and December 2014 to compare clinical outcomes of patients with long-term urinary catheterization as those without CAUTI, those with non-ESBL Enterobacteriaceae CAUTI, and those with ESBL Enterobacteriaceae CAUTI.

Results: There were 9,726 patients with urinary catheterization and 4,176 of those were categorized as patients with long-term urinary catheterization. Among the patients with long-term urinary catheterization, 207 patients developed CAUTI (4.96%). The causatives were Enterobacteriaceae (179; 86%), *Staphylococcus aureus* (10; 5%), non-fernetator gram negative Bacilli (10; 5%), and *Candida* spp. (8; 4%). Of those with Enterobacteriaceae CAUTI, there were 101 patients (56%) infected with ESBL strains. The patients with ESBL CAUTI had higher mortality, hospital cost, and longer hospital stay than those infected with non-ESBL. Retention of other medical devices, immunocompromised status, emergent indication for admission, and initial admission to an intensive care unit were associated with non-ESBL and ESBL Enterobacteriaceae CAUTI. Previous antibiotic use was associated with the emergence of ESBL Enterobacteriaceae CAUTI. Only invasive procedures/operations, previous use of fluoroquinolones, broad spectrum cephalosporins, and beta-lactamase inhibitor antibiotics were associated with the ESBL Enterobacteriaceae CAUTI.

Conclusion: The patients with ESBL CAUTI had worst outcomes including mortality, hospital costs, and length of stay than those with non ESBL CAUTI. Invasive procedures/operations, previous use of fluoroquinolones, broad spectrum cephalosporins, and beta-lactamase inhibitor antibiotics were associated with the ESBL Enterobacteriaceae CAUTI in long-term catheterization.

Keywords: Long-term urinary catheterization, Catheter associated urinary tract infection, Extended spectrum beta-lactamase producing

Catheter associated urinary tract infection (CAUTI) is recognized as one of the important nosocomial infections[1,2]. The CAUTI rates reported in 2011 for facilities reporting to the National Healthcare Safety Network (NHSN) were 0.2 to 4.8 per 1,000 catheter-days for adult inpatient units[3]. One study reported that CAUTI increases hospital mortality and hospital costs[4]. The duration of catheterization is the most important risk factor for developing infection[5-8]. Approximately 12% to 16% of adult hospital inpatients will have an indwelling urinary catheter at some time during their hospitalization, and each day the indwelling urinary catheter remains, a patient has a 3% to 7% increased risk of acquiring a CAUTI[9]. According to the nature of the nosocomial

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infection, the causative pathogens are likely to be multi-drug resistant organisms[10-12], and then the optional antibiotics are limited. Furthermore, the potential biofilm formation due to retention of urinary device causes unfavorable clinical outcomes[13]. In recent years, extended-spectrum beta-lactamase (ESBL) Enterobacteriaceae have emerged worldwide as one of the important pathogenic organisms of nosocomial infection[14]. These organisms are also the major cause of CAUTI. It is known that the major risk factors for ESBL CAUTI infection are male sex, preexisting urinary tract disease, having a urinary tract procedure, and longer duration of catheterization prior to CAUTI onset[15]. A recent study has suggested several strategies to decrease CAUTI including the use of retained catheters only with appropriate indications and leaving them in place only as long as needed[16]. However, these recommendations cannot be applied to patients with specific conditions who need long-term urinary catheterization, for example patients with urinary tract obstruction or patients with spinal cord injury. These patients are most at risk for infection with multi-drug resistant organisms including ESBL Enterobacteriaceae. Unfortunately, data on CAUTI among these patients is still scanty, so specific recommendations for reducing the risk in these populations is also limited. In the present study, the authors conducted a retrospective cohort study in patients with long-term urinary catheterization to study the clinical outcomes, economic burden, and risk factors of those who develop ESBL Enterobacteriaceae CAUTI.

Materials and Methods
Setting
The present study was conducted at Songklanagarind Hospital, a tertiary-care hospital in southern Thailand with 800 patient beds and approximately 29,000 admissions per year. The hospital has a computerized database of demographic information, clinical data, and hospital costs of all patients. The hospital has continual surveillance for nosocomial infections. The details of antibiotic costs are recorded in the database of the pharmaceutical unit. The data compiled from the surveillance, including information on microbiological laboratory results, antibiotic use, interventions, and placement of medical devices for the patients who contract a nosocomial infection were also recorded into the hospital database.

Study design
The study protocol was approved by the

Institutional Review Board (IRB) of the Faculty of Medicine (#EC: 58-094-14-1). This was a retrospective cohort study to compare clinical outcomes among three groups of patients with long-term urinary catheterization, those without CAUTI, those with non-ESBL Enterobacteriaceae CAUTI, and those with ESBL Enterobacteriaceae CAUTI. Long-term urinary catheterization was defined as a patient older than 15 years old with an indwelling Foley catheter or suprapubic cystostomy more than 14 days. CAUTI patients were defined as 1) having an indwelling urinary catheter in place for more than two days on the date of the event, at the time of diagnosis of CAUTI, 2) having at least one of the following signs or symptoms at the time of CAUTI diagnosis such as fever, suprapubic tenderness, costovertebral angle pain or tenderness, and 3) a urine culture with no more than two species of organisms identified, at least one of which was a bacterium of more than 105 CFU/mm$^{3(17)}$. The risk factors for CAUTI was the primary outcome of the current study and clinical outcomes including economic burden was the secondary outcome.

Microbiology
Enterobacteriaceae were identified on the basis of standard biochemical reactions from clinical specimens submitted to the microbiology laboratory. Minimal inhibitory concentration (MIC) of antibiotics were tested using methods and interpreted according to CLSI guideline[18].

Data collection
The study was conducted in patients with long-term urinary catheterization in Songklanagarind Hospital between January 2010 and December 2014. The medical records of all study patients were reviewed. Information extracted included age, sex, underlying diseases or comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II score, presence of diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, chronic kidney diseases, HIV infection and other indications of immune compromised status such as neutropenia or receiving immunosuppressive therapy (receipt of cytotoxic agents within six weeks or corticosteroids at a dosage equivalent to or higher than 10 mg of prednisolone daily for more than five days within four weeks prior to the onset of CAUTI, experience of neutropenia (absolute neutrophil count of less than 0.5 ×10^9 neutrophils/L), receiving an instrumentation or invasive procedure such as bronchoscopy, gastroscopy or tissue biopsy from

visceral organs, indwelling intravascular devices, endotracheal tube, and tube drainage. Previous use of antibiotics was defined from documentation of an antibiotic prescription within three months prior to CAUTI, based on the database of the pharmaceutical unit and medical records.

Statistical analysis

Univariate analysis of potential risk factors for non-ESBL and ESBL CAUTI was performed using the chi-square test or Fisher's exact test for categorical variables, and one-way analysis of variance Kruskal-Wallis test for continuous variables. Variables with p-value of less than 0.2 and other clinically relevant variables were then included in the initial multinomial logistic regression model. The control group was set as the referent level against CAUTI cases. In another model, non-ESBL cases were used as the referent group to check for consistency of risk factors for ESBL-UTI cases. Adjusted relative risk ratios (RRR) and 95% confidence intervals (CI) were used. All p-values were two tailed and significance was set at less than 0.05.

All analyses were conducted using Epicalc package in R statistical software and environment (version 2.14.2) Songkhla, Thailand.

Results

There were 9,726 patients with urinary catheterization recorded in the computerized database of Songklanagarind Hospital. Of these patients, 4,176 were categorized as having long-term urinary catheterization. The demographic data and clinical features of these patients is shown in Table 1. Among the patients with long-term urinary catheterization, 207 patients were classified as having developed CAUTI (4.96%). The causative pathogens identified as the causes of CAUTI were Enterobacteriaceae (179; 86%), *Staphylococcus aureus* (10; 5%), non-fermentator gram negative Bacilli (10; 5%), and *Candida* spp. (8; 4%). Of those with Enterobacteriaceae CAUTI, 101 patients (56%) were infected with ESBL strains *Escherichia coli* (54; 53%), *Klebsiella pneumoniae* (40; 40%), and other (7; 7%). Of the 78 patients with non-ESBL Enterobacteriaceae CAUTI, the causative organisms were *E. coli* (43; 55%), *K. pneumonia* (33; 42%) and other (2; 3%). Comparisons of the clinical outcomes are shown in Table 2. The patients with ESBL CAUTI had higher mortality, hospital costs, and longer hospital stay than those infected with non-ESBL CAUTI. The major cause of mortality of the patients with ESBL CAUTI was other site

Table 1. Demographic data and clinical features of the 4,176 patients with long-term urinary catheterization

Variables	n = 4,176
	n (%)
Age (years), Median (IQR)	49 (24, 69)
Range	15 to 91
Sex: female	1,912 (46)
Comorbidities	1,592 (38)
Diabetes mellitus	368 (8)
Arterial hypertension	206 (5)
Cardiovascular diseases	120 (3)
Cerebrovascular diseases	110 (3)
Chronic kidney diseases	36 (1)
Spine injury/surgery	288 (7)
At least 1 comorbidity	464 (11)
Immunocompromised status	30 (0.7)
Emergent indication for admission	1,717 (41)
Initial admission to intensive care units	450 (11)
Admission wards	
Medical	1,942 (47)
Surgical	2,066 (48)
Other	363 (5)
Time period of admission	
January 2010 to December 2010	650 (16)
January 2011 to December 2011	789 (18)
January 2012 to December 2012	901 (22)
January 2013 to December 2013	891 (21)
January 2014 to December 2015	945 (23)
Retention of other medical devices	1,336 (32)
Intravascular devices	335 (8)
Mechanical ventilator	956 (23)
Other	45 (1)
Invasive procedures/operations	2,273 (54)
Gastrointestinal endoscopy	102 (2)
Bronchoscopy	198 (5)
Urinary endoscopy	94 (2)
Operations	1,879 (45)
Initial APACHE II score, Median (IQR)	14 (10, 17)
Urinary catheterization day, Median (IQR)	22 (18, 36)
Suprapubic cystostomy	450 (11)

IQR=interquartile range; APACHE II=Acute physiology and chronic health evaluation

Table 2. Comparisons of outcomes for the patients without CAUTI and patients with non-ESBL and ESBL CAUTI

Outcomes	Value for the patients without CAUTI (n = 3,969)	Value for the patients with non-ESBL Enterobacteriaceae CAUTI (n = 78)	p-value[a]	Value for the patients with ESBL Enterobacteriaceae CAUTI (n = 101)	p-value[b]	p-value[c]
Mortality, n (%)						
In-hospital	105 (2.6)	4 (5.1)	0.182	13 (12.9)	<0.001	<0.001
Due to CAUTI	0 (0.0)	2 (2.6)	<0.001	2 (2.0)	0.804	<0.001
Due to other infections	32 (0.8)	1 (1.3)	0.645	11 (10.9)	<0.001	<0.001
Due to non-infection	73 (1.8)	1 (1.3)	0.718	1 (1.0)	0.856	0.536
Length of hospital stay after infection (days), Median (IQR)	18 (13, 25)	19 (14, 26)	0.235	25 (21,30)	0.032	0.004
Cost (baht*), Median (IQR)						
Total hospital	79,456 (52,136, 84,256)	89,665 (62,315, 92,563)	0.032	118,785 (92,564, 151,265)	0.042	<0.001
Antimicrobial	10,769 (9,568, 12,458)	29,568 (21,895, 32,695)	<0.001	40,687 (36,215, 53,265)	0.025	<0.001
Non-antimicrobial	65,235 (60,524, 70,895)	65,784 (56,444, 71,456)	0.874	72,894 (68,561, 96,532)	0.002	<0.001

ESBL=extended-spectrum β-lactamase-producing; CAUTI=catheter associated urinary tract infection; IQR=interquartile range

[a] Value for the patients without CAUTI versus Value for the patients with non-ESBL CAUTI

[b] Value for the patients without CAUTI versus Value for the patients with ESBL CAUTI

[c] Value for the patients with non-ESBL CAUTI versus Value for the patients with ESBL CAUTI

* 1 U.S. dollar=31 baht (as of July, 2017)

infections, accounting for 84% of all mortalities. The other site infections included pneumonia (8; 73%), primary bacteremia (1; 9%), soft tissue infection (1; 9%) and intraperitoneal infection (1; 9%). The causative organisms for those infections were carbapenem-resistant *Acinetobacter baumannii* (8; 73%), *Pseudomonas aeruginosa* (1; 0.3%), methicillin-resistant *S. aureus* (1; 0.9%), and *Candida albicans* (1; 0.9%).

From the multinomial logistic regression analysis (Table 3), retention of other medical devices, immunocompromised status, emergent indication for admission and initial admission to an intensive care unit were associated with both non-ESBL and ESBL Enterobacteriaceae CAUTI. Invasive procedures and operations were associated with only ESBL Enterobacteriaceae CAUTI. For previous antibiotic use, previous use of aminoglycosides (gentamicin and amikacin), fluoroquinolones (norfloxacin, ofloxacin, ciprofloxacin, levofloxacin, and moxifloxacin), broad-spectrum cephalosporins (ceftriaxone, cefotaxime, ceftazidime, cefixime, and cefoperazone/sulbactam), carbapenems (ertrapenem, imipenem/cilastatin, and meropenem) and beta-lactamase inhibitor antibiotics (amoxicillin/clavulonic acid, piperacillin/tazobactam, and cefoperazone/sulbactam) were associated with the emergence of ESBL Enterobacteriaceae CAUTI. Only invasive procedures/operations, previous use of fluoroquinolones, broad-spectrum cephalosporins, and beta-lactamase inhibitor antibiotics were associated with ESBL Enterobacteriaceae CAUTI.

Discussion

The present study showed that ESBL Enterobacteriaceae CAUTI among patients with long-term urinary catheterization had unfavorable outcomes including higher mortality, hospital costs, and increased length of stay.

Several conditions were identified as associated with CAUTI infection including invasive procedures/operations and previous use of several antibiotics, which may have contributed to the increased risk due to the patients' vulnerability and therefore, the need for these devices. Several antibiotic groups examined, notably fluoroquinolones, broad-spectrum cephalosporins, and beta-lactamase inhibitor antibiotics were associated with ESBL Enterobacteriaceae CAUTI.

CAUTI among the patients with long-term urinary catheterization was relatively high and caused by antibiotic resistant organisms. These findings can be explained by, first, most patients with long-term urinary catheterization were elderly and had multiple comorbidities, second, long-term catheterization leads to bacterial colonization and biofilm formation, and third, patients were usually exposed to antibiotics during hospitalization.

Table 3. Relative risk ratios (RRR) for non-ESBL and ESBL Enterobacteriaceae CAUTI

Variables	Value for the patients without CAUTI (n = 3,969)	Value for the patients with non-ESBL Enterobacteriaceae CAUTI (n = 78)	Value for the patients with ESBL Enterobacteriaceae CAUTI (n = 101)	A: RRR (95% CI)	B: RRR (95% CI)	C: RRR (95% CI)
Age (years), Median (IQR)	47 (28, 62)	48 (30, 69)	49 (31, 71)	1.0 (0.8 to 1.3)	1.0 (0.8 to 1.2)	1.1 (0.9 to 1.4)
Female	1,890 (48)	38 (49)	50 (50)	1.0 (0.8 to 1.3)	1.0 (0.8 to 1.4)	1.0 (0.9 to 1.3)
Comorbidities	399 (10)	9 (12)	12 (12)	1.1 (0.6 to 2.1)	1.0 (0.5 to 2.9)	1.2 (0.7 to 2.0)
Retention of other medical devices	1,200 (30)	32 (41)	54 (53)	1.4 (1.0 to 1.8)	1.3 (0.9 to 1.8)	1.8 (1.5 to 2.1)*
Immunocompromised	12 (0.3)	4 (5)	6 (6)	17.0 (5.6 to 51.4)	1.1 (0.3 to 4.0)	19.6 (7.5 to 51.3)*
Emergency admission	1,560 (39)	45 (58)	72 (71)	1.5 (1.2 to 1.8)*	1.2 (0.5 to 1.5)	1.8 (1.6 to 2.1)*
Initial admission to ICU	320 (8)	12 (15)	23 (23)	1.9 (1.1 to 3.2)*	1.4 (0.8 to 2.8)	2.8 (1.9 to 4.1)*
Invasive procedures/operations	1,955 (49)	45 (58)	79 (78)	1.2 (0.9 to 1.4)	1.4 (1.1 to 1.7)*	1.6 (1.4 to 1.8)*
Catheterization day, Median (IQR)	20 (15, 34)	23 (17, 37)	23 (17, 39)	1.4 (0.9 to 1.8)	1.0 (0.7 to 1.3)	1.5 (0.9 to 1.9)
APACHE II score, Median (IQR)	14 (9, 16)	15 (10, 18)	15 (10, 19)	1.3 (0.8 to 1.6)	1.0 (0.8 to 1.2)	1.3 (0.9 to 1.7)
Suprapubic cystostomy	403 (10)	8 (10)	11 (11)	1.0 (0.5 to 2.0)	1.0 (0.4 to 2.5)	1.1 (0.6 to 1.9)
Previous use antibiotics						
Penicillin	205 (5)	5 (6)	7 (7)	1.2 (0.5 to 2.9)	1.1 (0.4 to 3.3)	1.3 (0.6 to 2.8)
Aminoglycoside	123 (3)	4 (5)	9 (9)	1.7 (0.6 to 4.4)	1.7 (0.6 to 5.4)	2.9 (1.5 to 5.5)*
Fluoroquinolone	223 (6)	6 (8)	20 (20)	1.4 (0.6 to 3.0)	2.6 (1.1 to 6.1)*	3.5 (2.3 to 5.3)*
Broad-spectrum cephalosporin	389 (10)	9 (12)	38 (38)	1.2 (0.6 to 2.2)	3.2 (1.7 to 6.3)*	3.8 (2.9 to 5.0)*
Carbapenem	68 (2)	2 (3)	9 (9)	1.5 (0.4 to 6.0)	3.5 (0.8 to 15.6)	5.2 (2.7 to 10.1)*
Beta-lactamase inhibitor antibiotic	101 (3)	4 (5)	16 (16)	2.0 (0.8 to 5.3)	3.1 (1.1 to 8.9)*	6.2 (3.8 to 10.2)*

ESBL=extended-spectrum β-lactamase-producing; CAUTI=catheter associated urinary tract infection; IQR=interquartile range; APACHE II=Acute physiology and chronic health evaluation

A: Value for the patients without CAUTI versus Value for the patients with non-ESBL CAUTI

B: Value for the patients without CAUTI versus Value for the patients with ESBL CAUTI

C: Value for the patients with non-ESBL CAUTI versus Value for the patients with ESBL CAUTI

In the present study, the proportion of ESBL Enterobacteriaceae as the causative pathogen was relatively high, a finding that supports the global trend of emerging resistance among these organisms[19,20].

However, the relatively high incidence of ESBL Enterobacteriaceae CAUTI in the present study was likely related to the study setting, a tertiary care hospital in which most of the patients had pre-existing risk factors for ESBL Enterobacteriaceae infection[21].

The present findings on the higher risk of poor outcomes and higher economic burdens of patients with ESBL Enterobacteriaceae UTI were consistent with several reports[22]. It was interesting that the commonest cause of mortality for the patients with ESBL Enterobacteriaceae CAUTI was other site infections beyond urinary tract infection, which may have been due to the increased susceptibility of the present patient population to infection. The data showed that carbapenem resistant *A. baumannii* (CRAB) were the most common organisms involved in those infections. Patients with ESBL Enterobacteriaceae CAUTI had a higher risk to develop a CRAB infection due to the common risk factors for ESBL Enterobacteriaceae and CRAB infection such as 1) the exposure of sufficient antibiotics for treatment of ESBL Enterobacteriaceae, especially carbapenems, 2) interventions during an ESBL Enterobacteriaceae infection such as implantation of a medical device, use of a mechanical ventilator, or transference to an intensive care unit, 3) patients receiving advance surgery such as chemotherapy and empirical treatment with broad spectrum antibiotics as the present study was conducted only in a tertiary care hospital, and 4) the prevalence of *A. baumannii* infection is geographically dependent and relatively high in tropical region[23-26].

It is not surprising that retention of other medical devices, performing of intensive procedures and

operations were associated with both non-ESBL and ESBL Enterobacteriaceae CAUTI. The findings can be explained by noting the two major routes of CAUTI, direct exposure of the urinary tract to a hospital environment in which colonizing with both non-ESBL and ESBL Enterobacteriaceae is common, and hematogenous spreading of Enterobacteriaceae from the sites of invasive procedures, operations, and other medical devices. The present study also found that suprapubic cystostomy had no effect on infection by either non-ESBL or ESBL Enterobacteriaceae CAUTI. This finding also supports the results of a systematic review on the efficacy of suprapubic cystostomy to prevent CAUTI[27]. This result may be due because cystostomy can correct urinary tract obstruction, so it reduces CAUTI.

The present findings on the association between the use of several common antibiotics and the development of ESBL Enterobacteriaceae CAUTI are consistent with a previous report[28]. The selective pressure was not observed among the patients treated with penicillin, as most of the existing microbiota, such as those in the gut and oropharynx, are already resistant to these antibiotics[29]. This explanation is additionally supported by the lack of any association between exposure to those antibiotics and non-ESBL Enterobacteriaceae CAUTI. Thus, most non-ESBL Enterobacteriaceae strains in the study setting were susceptible to aminoglycosides, fluoroquinolones, and broad-spectrum cephalosporins.

It is interesting that the previous use of carbapenems increased the risk of ESBL Enterobacteriaceae CAUTI, even though theoretically these organisms can be eradicated with carbapenems. There are three plausible explanations for this. First, ESBL Enterobacteriaceae had longer killing times for carbapenems than those of normal flora and non-ESBL Enterobacteriaceae. Second, carbapenems are selective pressure to promote growth of bacteria carrying mobile genetic elements for ESBL phenotypes which pass to Enterobacteriaceae causing infection with ESBL strains. And third, it is possible to emerge of sub-population of carbapenem resistant Enterobacteriaceae prior to exposure of carbapenems.

There are several limitations to the present study that should be acknowledged. First, according to the nature of a retrospective study, the results were confounded with several unmeasured variables, such as indications of previous antibiotic use and antibiotic exposure before hospitalization, and indication for Foley catheter insertion. Second, with the limited sample size, multivariate analysis was not conducted to explore interactions between interesting variables. Third, antibiotics in each group had relatively wide range of spectrum assuming different effect on selective pressure. Fourth, according to the inhomogeneous of organism, the data of mortality among patient with other CAUTI (not Enterobacteriaceae) infection were not included in the analysis. Last, the high mortality among the patients with CAUTI due to ESBL Enterobacteriaceae might be contributed by other confounding factors including superimposed infection due to carbapenem resistant organism for example CRAB.

In conclusion, CAUTI due to ESBL Enterobacteriaceae yielded unfavorable clinical outcomes and caused economic burdens. Prolonged catheterization increased CAUTI due to ESBL Enterobacteriaceae. Antibiotic use is one of the important factors driving this infection.

What is already known on this topic?

ESBL Enterobacteriaceae are also the major cause of CAUTI. The risk factors are male sex, preexisting urinary tract disease, having a urinary tract procedure, and longer duration of catheterization prior to CAUTI onset.

No study of outcome of CAUTI in long-term catheterization was done.

What this study adds?

This is the first study that define long-term catheterization (more than 15 days) and study the outcomes and risk factors of ESBL CAUTI in long-term urinary catheterization.

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Conflicts of interest

The authors declare no conflict of interest.

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