INCIDENCE AND RISK FACTORS OF EXTENDED SPECTRUM BETA-LACTAMASE-PRODUCING *E.coli* AMONG INPATIENTS WITH NOSOCOMIAL URINARY TRACT INFECTION AT TAKSIN HOSPITAL, BANGKOK METROPOLITAN ADMINISTRATION

SOMYING TIPMONGKOL

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE (PUBLIC HEALTH)
PROGRAM IN INFECTIOUS DISEASE AND EPIDEMIOLOGY
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2015

Thesis
entitled

INCIDENCE AND RISK FACTORS OF EXTENDED SPECTRUM BETA-LACTAMASE-PRODUCING *E.coli* AMONG INPATIENTS WITH NOSOCOMIAL URINARY TRACT INFECTION AT TAKSIN HOSPITAL, BANGKOK METROPOLITAN ADMINISTRATION

.....
Mrs. Somying Tipmongkol
Candidate

.....
Assoc. Prof. Kulaya Narksawat,
D.D.S., M.Sc.(Medical Epidemiology)
Major advisor

.....
Assoc. Prof. Dusit Sujirarat,
M.Sc.(Biostatistics)
Co-advisor

.....
Miss Supunnee Jirajariyavej,
M.D., Dip. Internal Medicine in Infectious Diseases
Co-advisor

.....
Prof. Patcharee Lertrit,
M.D., Ph.D.(Biochemistry)
Dean
Faculty of Graduate Studies
Mahidol University

.....
Lect. Supawadee Boonchuen,
Ph.D.(Tropical Medicine)
Program Director
Master of Science (Public Health)
Program in Infectious Diseases and Epidemiology
Faculty of Public Health
Mahidol University

Thesis
entitled

INCIDENCE AND RISK FACTORS OF EXTENDED SPECTRUM BETA-LACTAMASE-PRODUCING *E.coli* AMONG INPATIENTS WITH NOSOCOMIAL URINARY TRACT INFECTION AT TAKSIN HOSPITAL, BANGKOK METROPOLITAN ADMINISTRATION

was submitted to the Faculty of Graduate Studies, Mahidol University
for the degree of Master of Science (Public Health)
Program in Infectious Diseases and Epidemiology
on
April 20, 2015

.....
Mrs. Somying Tipmongkol
Candidate

.....
Mrs. Kittiya Srilerdfa,
M.D., M.P.A.(Public Administration)
Chair

.....
Assoc. Prof. Kulaya Narksawat,
D.D.S., M.Sc.(Medical Epidemiology)
Member

.....
Miss Supunnee Jirajariyavej,
M.D., Dip. Internal Medicine in Infectious Diseases
Member

.....
Assoc. Prof. Dusit Sujirarat,
M.Sc.(Biostatistics)
Member

.....
Prof. Patcharee Lertrit,
M.D., Ph.D.(Biochemistry)
Dean
Faculty of Graduate Studies
Mahidol University

.....
Assoc. Prof. Prayoon Fongsatitkul,
Ph.D.(Environment Engineering)
Dean
Faculty of Public Health
Mahidol University

ACKNOWLEDGEMENTS

I would like to express my appreciation to my major thesis advisor, Associate Professor Kulaya Narksawat, for her invaluable help, supervision, guidance, construction critisim, and constant encouragement throughout the course of this research. I am most grateful for her teaching and advice. I would not have achieved this far and this thesis would not have been completed without all the support that I have always received from her. In addition, I am grateful for my co-advisors, Associate Professor Dusit Sujirarat, Dr. Supunnee Jirajariyavej, and Dr. Thanawat Imsomboon for suggestions, helpful guidance and all their help.

My special thanks, Dr. Kittiya Srilerdfa, the external examiner of thesis defence, and her kindness for the suggestion for this research. I also want to thank the assistant lectures, and the staff of the Epidemiology Department, Faculty of public Health, Mahidol University.

Finally, I most heartedly thank to my parents and my friends for all their supports throughout the period of this research.

This research was partially founded by Mahidol University Alumni Association under the Royal Patronage of His Majesty the King academic year 2013.

Somying Tipmongkol

INCIDENCE AND RISK FACTORS OF EXTENDED SPECTRUM BETA-LACTAMASE-PRODUCING *E.coli* AMONG INPATIENTS WITH NOSOCOMIAL URINARY TRACT INFECTION AT TAKSIN HOSPITAL, BANGKOK METROPOLITAN ADMINISTRATION

SOMYING TIPMONGKOL 5436095 PHPH/M

M.Sc.(PUBLIC HEALTH) PROGRAM IN INFECTIOUS DISEASES AND EPIDEMIOLOGY

THESIS ADVISORY COMMITTEE: KULAYA NARKSAWAT, D.D.S., M.Sc. (MEDICAL EPIDEMIOLOGY), DUSIT SUJIRARAT, M.Sc.(BIOSTATISTICS), SUPUNNEE JIRAJARIYAVEJ, M.D., DIP. INTERNAL MEDICINE IN INFECTIOUS DISEASES

ABSTARCT

A retrospective cohort study was conducted to assess incidence density and factors associated with nosocomial urinary tract infection by ESBL-producing *E.coli* among patients admitted at Taksin hospital, Bangkok Metropolitan Administration, from 1st January to 31th December 2011. Data collection was performed by retrieving from medical records. Among total number of 937 inpatients with urinary tract infection, the gender ratio (male: female) was 1:1.2, with average age 56.9±23.5 years. Sixty five point three percent of them were from medical ward, 11.8 percent from surgical ward, 11.5 percent from intensive care unit and the rest 11.3 percent from ob-gyn ward. The total person-week of study population was 1,644 weeks, overall incidence density of nosocomial urinary tract infection by ESBL-producing *E.coli* was 5.1 per 100 per week. Results obtained from Cox's regression analysis revealed that significant risk factors were being female (HR=1.67 95%CI; 1.01-2.76), having chronic diseases (HR=3.02 95%CI; 1.91-4.78), using prior antibiotic during last year (HR= 3.02 95%CI; 1.58-5.77), staying in other wards not ICU (HR=8.85 95%CI; 1.21-64.47), using urine catheter (HR=1.63 95%CI; 1.01-2.62), having invasive urine catheter (HR=1.76 95%CI; 1.13-2.70) and using antibiotic during present admission (HR=9.82 95%CI; 3.02-31.97)

This study suggests that the appropriate use of the antibiotics for the treatment of infection are important for better clinical care. The history of antibiotics used are important for better treatment. The practice in accordance with the standard control is highly recommended for the prevention and the protection of multidrug resistance in the hospital. Antibiotic drugs administration is strongly recommended for its proper and effective utilization regimen based on antibiogram and sensitivity report to avoid a development of undesirable drug resistance.

KEY WORDS: NOSOCOMIAL URINARY TRACT INFECTION / ESBL PRODUCING-*E.coli* / RISK FACTORS

85 pages

อุบัติการณ์และปัจจัยเสี่ยงของการติดเชื้อ *E.coli* ที่สร้าง ESBL ในผู้ป่วยในที่มีการติดเชื้อระบบทางเดินปัสสาวะ โรงพยาบาลตากสิน สำนักการแพทย์ กรุงเทพมหานคร

INCIDENCE AND RISK FACTORS OF EXTENDED SPECTRUM BETA-LACTAMASE-PRODUCING *E.coli* AMONG INPATIENTS WITH NOSOCOMIAL URINARY TRACT INFECTION AT TAKSIN HOSPITAL BANGKOK METROPOLITAN ADMINISTRATION

สมหญิง ทิพย์มงคล 5436095 PHPH/M

วท.ม.(สาธารณสุขศาสตร์) สาขาวิชาโรคติดเชื้อและวิทยาการระบาด

คณะกรรมการที่ปรึกษาวิทยานิพนธ์: กุลยา นาคสวัสดิ์, D.D.S., M.P.H., M.Sc., ดุสิต สุจิรารัตน์, M.Sc. (BIOSTATISTICS), สุพรรณี จิรจริยาเวช, M.D., DIP. INTERNAL MEDICINE IN INFECTIOUS DISEASES

บทคัดย่อ

การศึกษา retrospective cohort นี้เพื่อศึกษาอุบัติการณ์และปัจจัยที่เกี่ยวข้องกับการติดเชื้อระบบทางเดินปัสสาวะในโรงพยาบาลจากเชื้อ *E.coli* ที่สร้าง ESBL โดยรวบรวมข้อมูลจากเวชระเบียนของ ผู้ป่วยในโรงพยาบาลตากสิน สำนักการแพทย์ กรุงเทพมหานคร ระหว่างวันที่ 1 มกราคม ถึงวันที่ 31 ธันวาคม 2554 จำนวน 937 ราย โดยมีอัตราส่วนเพศชายต่อเพศหญิงเท่ากับ 1: 1.2 อายุเฉลี่ย 56.9 ± 23.5 ปี ร้อยละ 65.3 นอนพักรักษาตัวในแผนกอายุรกรรม ร้อยละ 11.8 นอนพักรักษาตัวในแผนกศัลยกรรม ร้อยละ11.5 นอนพัก รักษาตัวในไอซียูและร้อยละ11.3 พักรักษาตัวในแผนกสูติ-นรีเวชกรรม

อัตราอุบัติการณ์รวมของการติดเชื้อเท่ากับ 5.1 ต่อ 100 คนต่อสัปดาห์ ผลการวิเคราะห์ด้วย Cox's regression พบว่าปัจจัยที่มีความสัมพันธ์กับการติดเชื้อระบบทางเดินปัสสาวะในโรงพยาบาลจากเชื้อ *E.coli* ที่สร้าง ESBL ได้แก่ การเป็นเพศหญิง (HR= 1.67 95%CI; 1.01-2.76) การมีโรคเรื้อรังเป็นโรคร่วม (HR= 3.02 95%CI; 1.91 -4.78) ผู้ที่เคยใช้ยาปฏิชีวนะภายใน 1 ปี (HR= 3.02 95%CI; 1.58-5.77) พักรักษาตัว ในหอผู้ป่วยอื่นที่ไม่ใช่ ICU (HR= 8.85 95%CI; 1.21-64.47) ผู้ที่เคยใส่สายสวนปัสสาวะภายใน 30 วันก่อนการนอนโรงพยาบาลครั้งนี้ (HR= 1.63 95%CI; 1.01-2.62) ผู้ที่ได้รับการรักษาด้วยการใส่สายสวนปัสสาวะ (HR= 1.76 95%CI; 1.13-2.70) และการ ใช้ยาปฏิชีวนะในการรักษาครั้งนี้ (HR= 9.82 95%CI; 3.02-31.97) จากผลการวิจัยนี้เสนอแนะว่าควรให้ความสำคัญ กับการใช้ยาปฏิชีวนะ อย่างเหมาะสมในการรักษาการ ติดเชื้อในโรงพยาบาล ร่วมกับการใช้ประโยชน์จากการ รายงานผลความไวของยาในใบรายงานผลตรวจเพาะเชื้อและ antibiogram เพื่อเป็นการใช้ยาปฏิชีวนะอย่าง เหมาะสม และมีประสิทธิภาพรวมทั้งการซักถามประวัติการได้รับยาปฏิชีวนะ นอกจากนั้นสิ่งที่ต้องปฏิบัติอย่าง เคร่งครัด เพื่อป้องกันการติดเชื้อดื้อยาในโรงพยาบาลคือ การปฏิบัติตามมาตรฐานการป้องกันและควบคุมการติดเชื้อของโรงพยาบาล

85 หน้า

CONTENTS

CONTENTS (cont.)

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES (cont.)

CHAPTER I
INTRODUCTION

1.1 Rationale and Background

Escherichia coli (E.coli) is a common gram negative bacteria which normally exist in the intestine and be necessary for digestion (1). Generally *E.coli* can get into tissues or organs that it does not belong to such as the urinary tract, and can lead to symptomatic infection which bladder infection is the most common site where antibiotics is necessary (1, 2). Extended spectrum beta-lactamases (ESBLs) are produced by gram negative bacteria, which are *Escherichia coli (E.coli)* and *Klebsilla pneumoniae (K.pneumoniae)* (3, 4), they have the ability to hydrolyze beta-lactam antibiotics (Broad-spectrum cephalosporins and aztreonam) (5). They are defined as plasmid-mediated enzymes that cephalosporins and monolactams. The ESBLs have various genotypes, most of them are in group extended-spectrum cephalosporins, monobactams (6).

Beta-lactamases are hydrolytic enzymes that can confer bacterial resistance to antibiotics, such as penicillins and cephalosporins. A major concern of the patients are prone to infection with drug resistance bacteria, especially gram negative bacteria which produce extended spectrum beta-lactamases (ESBLs), as a higher morbidity, mortality and institution of appropriate antimicrobial therapy (6).

In the early 1980, the ESBLs were first recognized, and found to be point mutations of broad spectrum enzymes which resulted in resistance to the beta-lactam of antibiotic (7, 8). The prevalence of bacteria producing ESBLs have become a serious cause of hospital-acquired infection worldwide, particularly in critical patients admitted in the intensive care unit (3, 9). The National Nosocomial Infections Surveillance System (NNIS) in Thailand reported that the prevalence of ESBLs occurred at ICU and non ICU were 5.8% and 1.5% respectively (10). The reports from South America showed rates of ESBLs ranked among the highest in the world. Surveillance data revealed alarmingly high prevalence of *E.coli* infection isolated in

Latin America ranging from 8.5% to 18% (11). Report from the SENTRY antimicrobial surveillance program 1998-1999 showed prevalence rate of ESBL producing *E.coli* in Asia were higher than other regions in the world isolates, ranged from 13% - 15% (12). In 2003, Sirisaj hospital reported the prevalence of ESBLs producing *E. coli* infection in 33.3% (15). Data obtained from Nan hospital during 2004-2010 indicated that the prevalence ESBL-producing *E.coli* were found in 21.9% from clinical specimens of patients attending Nan hospital and community hospital in Nan province, and 40.5% obtained from urine (13).The risk factors for hospital acquired associated ESBLs-producing *E.coli* infection found in ICU, prolonged hospitalization, used of ventilator mechanical, central venous indwelling, prior used of antibiotic, renal failure burns, urinary catheter and 3rd generation cephalosporin used (6). Rate of detection of ESBL-producing *E. coli* at Maharaj Nakorn Si Thamarat hospital during January to December 2010 was 11.30% (13 of 115) (14).

In 1983, the first outbreak involving ESBL-producing organisms in Germany where infections caused by these ESBL-producing organisms were identified. Since then it has been constantly growing of outbreak. At the present time it is widely recognized as clinical relevant causes of infections. ESBL-producing *E.coli* infection in hospital is associated with high rates of morbidity, mortality as well as health care costs (15).

ESBL-producing *E.coli* infections have been a significant worldwide nosocomial infection. Emergence of drug resistance strains is an alarming problem worldwide, especially where use of antibiotics is not strictly controlled. In Thailand, the drug smart used programs are uncommon and people can spend money for purchasing antibiotics without medical prescription, the rate of antibiotic resistance especially ESBL have significantly increased (15). Data obtains from department of Medicals Science, Ministry of Public Health showed that the prevalence of antibiotics resistance rate of ESBL-producing *E.coli* increased during the year 2000 to the year 2005. The prevalence of resistance rate of Ceftazidime increased from 13% to 23%, Cefotaxime from 20% to 33% and have been increased constantly in recent years (16). The infections from ESBL-producing *E.coli* responsible for 10 % up to 22% of urinary tract infection, 11% to 13% of bloodstream infection and 19% to 49 % of pneumonia (16).

Therefore ESBL-producing *E.coli* nosocomial infection is considered as the major health problem in Thailand and also in other countries. Data derived from Taksin hospital showed that the prevalence rate of ESBL-producing *E.coli* in urine increased during 2005-2011 from 2.88% to 30.44%. The infection from ESBL-producing *E.coli* in urine caused to secondary bloodstream infection and associated with a high mortality rate in hospital. The increasing associated with a high mortality rate, and also high cost of treatment including increasing of length of stay in hospital.

The purposes of this study are to indentify incidence and risk factors associated with ESBL-producing *E.coli* among inpatients with nosocomial infection at Taksin hospital, Bangkok Metropolitan Administration in 2011. The significant preventable risk factors from this study will be utilized for strengthening prevention and control strategies plan of ESBL-producing *E.coli* in Taksin hospital, Bangkok Metropolitan Administration (BMA).

1.2 Research Questions

1.2.1 What was the incidence density of ESBL–producing *E.coli* with nosocomial urinary tract infection among inpatients in 2011.

1.2.2 Were there any associations between nosocomial urinary tract infection by ESBL-producing *E.coli* and the following risk factors?

1) General characteristic: gender, age, department admitted and principle diagnosis for present admission
2) Prior antibiotics used within last year
3) Urine catheter used within 30 days
4) Recurrent urinary tract infections
5) Previous hospitalization
6) ICU stay during present admission
7) Patient’s co-morbidity
8) Invasive urine catheter used during present admission
9) Antibiotic used during this admission

1.3 Research Objectives

1.3.1 General Objectives

To assess incidence and risk factors associated with ESBL-producing *E.coli* among inpatients with nosocomial urinary tract infection at Taksin Hospital, Bangkok Metropolitan Administration in 2011.

1.3.2 Specific Objectives

1) To determine incidence of ESBL-producing *E.coli* with nosocomial urinary tract infection among inpatients.

2) To determine the association between nosocomial urinary tract infection by ESBL-producing *E.coli* and the following factors;

(1) General characteristic: gender, age, department admitted and principle diagnosis for present admission

(2) Prior antibiotics used within last year

(3) Urine catheter used within 30 days

(4) Recurrent urinary tract infections

(5) Previous hospitalization

(6) ICU stay during present admission

(7) Patient's co-morbidity

(8) Invasive urine catheter used during present admission

(9) Antibiotic used during the admission

1.4 Research Hypothesis

There were associations of nosocomial urinary tract infection by ESBL-producing *E.coli* with the following risk factors:

1.4.1 General characteristic: gender, age, department admitted and principle diagnosis for present admission

1.4.2 Prior antibiotics used within last year

1.4.3 Urine catheter used within 30 days

1.4.4 Recurrent urinary tract infections

1.4.5 Previous hospitalization

1.4.6 ICU stay during present admission

1.4.7 Patient's co-morbidity

1.4.8 Invasive urine catheter used during present admission

1.4.9 Antibiotic used during the admission

1.5 Research Variables

1.5.1 Independent Variable are including:

1) General characteristic are including:
   (1) Gender
   (2) Age
   (3) Department admitted
   (4) Principle diagnosis for present admission
2) Risk factors:
   (1) Prior antibiotics used within last year
   (2) Urine catheter used within 30 days
   (3) Recurrent urinary tract infections
   (4) Previous hospitalization
   (5) ICU stay during present admission
   (6) Patient's co-morbidity
   (7) Invasive urine catheter used during present admission
   (8) Antibiotic used during the admission

1.5.2 Dependent Variables

Having nosocomial urinary tract infection by ESBL-producing *E.coli*.

1.6 Operational Definitions

1.6.1 Patients with urinary tract infection referred to patients having urinary tract infection bladder, kidneys, urethers, or urethra after 48 hours of admission.

1.6.2 Department admitted referred to department or ward where patients had been admitted before having urinary tract infection.

1.6.3 Nosocomial infection referred to an infection occurred in a patient in a hospital or other health care facilities in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and also occupational infections among staffs of the facility. Nosocomial infections usually occur after 48 hours of admission (17).

1.6.4 Extended spectrum beta-lactamase referred to beta-lactamase enzyme which can confer bacteria resistance to all Penicillin, Cephalosporins group, and Aztreonam through their enzymatic hydrolysis of the four-atom ring (beta-lactam) of these antibiotics (6).

1.6.5 ESBL-producing *E.coli* referred to bacteria in strains of ESBL-producing *E.coli* which induce resistance to antimicrobial agents such as aminoglycosides; Gentamicin or third generation Cephalosporins; Cefotaxime or Ciprofloxacin (6).

1.6.6 Prior antibiotic use within last year referred previous taking any kind of antibiotics especially antimicrobial agents third-generation Cephalosporin: Ceftazidime, Ceftriaxone and Cefotaxime from hospitalization.

1.6.7 Recurrent urinary tract infection referred to having been diagnosed of recurrent urinary tract infection and receiving treatment within 90 days.

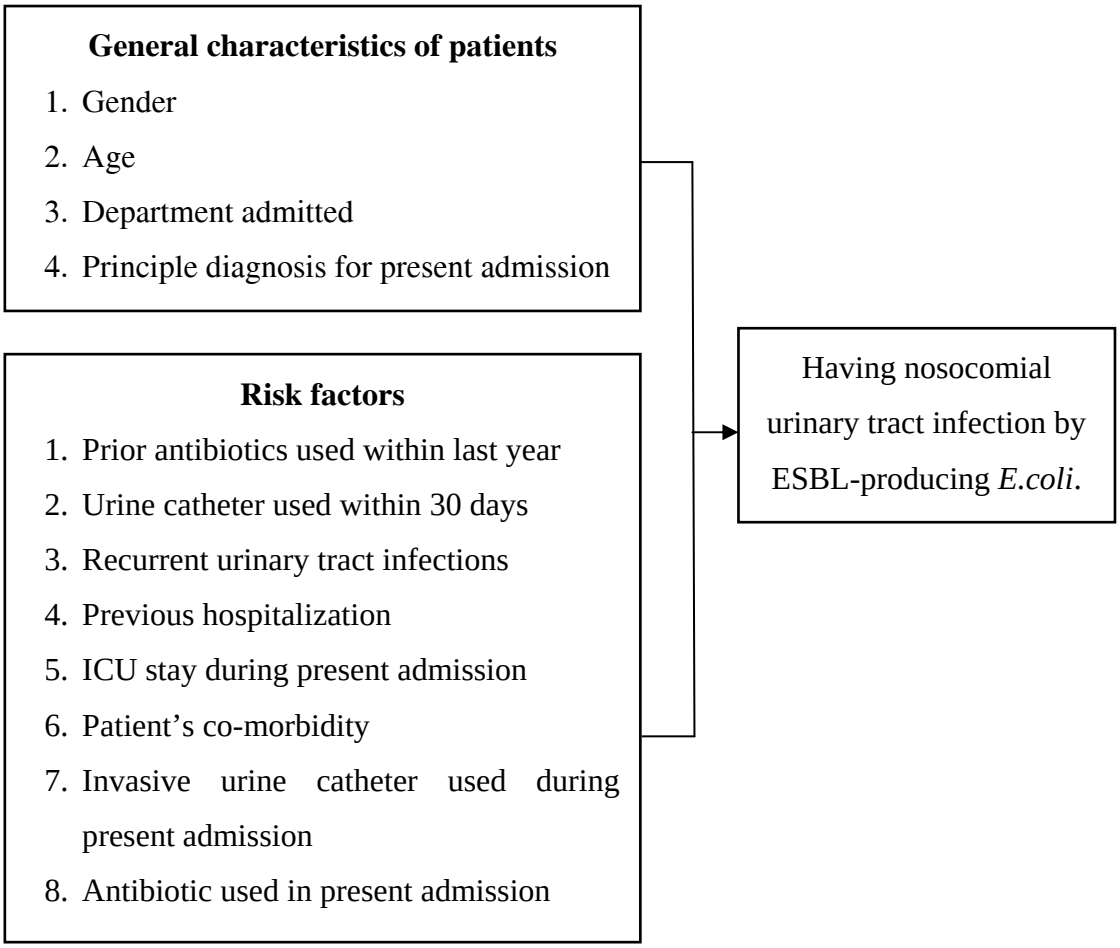
1.6.8 Previous hospitalization referred to previous admission from another healthcare sectors within a year before.

1.6.9 ICU stay during present admission referred to days of staying in ICU ward during present admission.

1.6.10 Patient's co-morbidity referred to having been diagnosed of co-morbidity and receiving treatment at the time of admission.

1.6.11 Invasive urine catheter used during present admission referred to invasive urine catheter used at the time of admission.

1.7 Conceptual Framework



CHAPTER II
LITERATURE REVIEW

The aims of this study were to identify risk factors associated with nosocomial urinary tract infection by extended spectrum beta-lactamase-producing *Escherichia coli* (ESBL-producing *E.coli*) among inpatients at Taksin hospital, Bangkok Metropolitan Administration. Review of literature includes the following:

2.1 Nosocomial infection and Urinary tract infections

2.1.1 Definition of nosocomial infection

2.1.2 Definition of urinary tract infection

2.2 Extended spectrum beta-lactamase-producing *E.coli*. (ESBL-producing *E.coli*)

2.2.1 Classification of ESBL- producing *E.coli*

2.2.2 History and epidemiology of ESBL- producing *E.coli*

2.2.2 Antibiotic resistance of ESBL- producing *E.coli*

2.2.3 Diagnosis and detection of ESBL- producing *E.coli*

2.2.4 Antimicrobial treatment of ESBL- producing *E.coli*

2.3 Related literature

2.1 Nosocomial infection and urinary tract infection

2.1.1 Definition of nosocomial infection

Nosocomial infections are important contributors to morbidity and mortality. They are more important public health problem with increasing economic and human impact. They are increasing numbers of the patients and frequent impaired immunity. Nosocomial infections are new organisms and increasing bacterial drugs resistance (17).

The World Health Organization (WHO) defined nosocomial infection (NI) or hospital- acquired infection (HAI) as "*An infection acquired in hospital by a patient who was admitted for a reason other than that infection (1). An infection occurring in a patient in a hospital or other health care facilities in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and also occupational infections among staffs of the facility"* (17, 18).

The nosocomial infections acquired during hospital care which are not present or incubating at admission, occurring more than 48 hours after admission. The infections have been developed for specific infection sites (e.g. urinary, respiratory, pulmonary) (19, 20). Nosocomial infections are considered either endemic or epidemic. Endemic infections are the most common. While epidemic infections occur during an unusual increase above the baseline of a specific infection or infecting organism, an outbreak.

The type of nosocomial infections are four most common types, urinary infections, surgical site infection, nosocomial pneumonia and nosocomial bacterimia. Urinary tract infections are the most common, 80% are associated with the used of an indwelling catheter. These infections are less associated with morbidity, but can lead to septicemia and death. About 0.5% to 15% of surgical infections are depending on the type of surgery and the patient's underlying disease. The indicator of surgical infection is the presence of purulent discharge around the wound or the insertion site of drain, or presence sign of cellulites. Nosocomial pneumonia is the significant problem. Approximately 3% of patients who has ventilators associated pneumonia can lead to a high fatality rate. The source of infections are endogenous and exogenous microorganism with transfer from respiratory equipments (15, 21).

The microorganisms, bacteria, viruses, fungi, and parasites, can causes of nosocomial infections and can be cross-infection. The normal flora bacteria are transmitted to sites outside of their normal environment can cause infection, occur with wound or with inappropriate antibiotic treatment that allows overgrowth of endogenous bacteria. The exogeneous bacteria cross infection can occur with transfer of microorganism from one patient or healthcare worker to another patient or healthcare worker. WHO summarizes mode of transmission between patients as

following statement: "*Bacteria are transmitted between patients: (a) through direct contact between patients hands, saliva droplets or other body fluids), (b) in the air (droplets or dust contaminated by a patient's bacteria), (c) via staff contaminated through patient care (hands, clothes, nose and throat) who become transient or permanent carriers, subsequently transmitting bacteria to other patients by direct contact during care, (d) via objects contaminated by the patient (including equipment), the staff's hands, visitors or other environment sources(e.g. water, other fluids, food)"* (17, 21). Another route of acquisition is normal flora from the healthcare environment. The microorganism may live in sterile products or disinfectants (Pseudomonas spp., Acenetobactor spp., Mycobacteriaceae), in damp areas, in water, in lines, in food, in fine dust, in droplet nuclei, in equipment and supplies use in care (21).

The NNIS system defined a nosocomial infection as a localized or systemic condition, resulting firstly from adverse reaction to the presence of the infection or its toxin, and secondly that was not present or incubating at the time of admission to the hospital (18).

CDC recommends two important principles upon which the nosocomial infection definitions are based. Firstly, the information used to determine the presence and the classification of infection should be a combination of the clinical findings and the results of laboratory tests. Clinical evidence is derived from direct observation, source of infection and reviews of the patient's record. Results of the laboratory tests include culture reports, antigen or antibody detection tests and microscopic visualization. Another data from the diagnostic tests that support and determine the classification of an infection are x-ray, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), radiolabeled scan, endoscopic procedure and biopsy or needle aspiration. Secondly, principle is the physician's diagnosis from direct observation during the treatment and clinical judgement utilizing the acceptable criteria for infection (18).

Infections are considered nosocomial infection in two special situations: the first one is acquired in the hospital but does not become evident before being discharged from the hospital. The second one is in a neonate that results from the passage through the birth canal. There are two special situations which are not

considered the nosocomial infection, one of which is associated with complication or extension of the infection already present on admission without a change in pathogens or symptoms associated with the acquisition of a new infection. In another situation, the infection is appearance at or before 48 hours after the birth, and acquired transplacentally for example toxoplasmosis, rubella, cytomegalovirus or syphilis (18).

Conditions that are not considered nosocomial infections are colonization which is the presence of microorganisms (on the skin, mucous membranes, in the opened wounds, excretion or secretion) that are not causing adverse clinical signs or symptoms and inflammation that results from tissue response to injury or stimulation by non infectious agents such as chemical (18).

2.1.2 Definition of urinary tract infection

The urinary tract infections, an infection of bladder, kidneys, ureters, or urethra are the most common nosocomial infections about 80% are associated with indwelling urine catheter (17). The infections occur when bacteria enter the urinary system. There are 4 portals of entry for microorganisms in urinary drainage systems: the urethral meatus-catheter junction; the catheter-drainage tubing junction; the drainage tubing-bag junction; and the outlet that drains urine from the bag (17).

CDC recommends the criteria for urinary tract infections diagnosis as following statement (19):

Definition: Symptomatic urinary tract infection must meet at least one of the following criteria:

Criterion 1: Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38°c), urgency, frequency, dysuria, or suprapubic tenderness and patient has a positive urine culture, that is, $\geq 10^5$ microorganisms per $cm.^3$ or urine with no more than two species of microorganisms.

Criterion 2: Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38°c), urgency, frequency, dysuria, or suprapubic tenderness and at least one of the following:

a. positive dipstick for leukocyte esterase and / or nitrate

b. pyuria (urine specimen with ≥10 wbc./mm.^{3} or ≥3 wbc./high power field of unspun urine)

c. organisms seen on gram stain of unspun urine

d. at least two urine cultures with repeated isolation of the same uropathogen (gram negative bacteria or *S.saprophyticus*) with ≥10^2 colonies/ml. in non voided specimens

e. ≥10^5 colonies/ml. of a single uropathogen (gram negative bacteria or *S.saprophyticus*) in a patient being treated with an effective antimicrobial agent for a urinary tract infection

f. physician diagnosis of a urinary tract infection

g. physician institutes appropriate therapy for a urinary tract infection.

Definitions: Asymptomatic bacteriuria

Criterion 1: Patient has had an indwelling urinary catheter within 7 days before the culture and patient has a positive urine culture, that is, ≥10^5 microorganisms per cm.^{3} of urine with no more than two species of microorganisms and patient has no fever (>38°c), urgency, frequency, dysuria, or suprapubic tenderness.

Criteria 2: Patient has not had an indwelling urinary catheter within 7 days before the first positive culture and patient has had a least two positive urine cultures, that is, ≥10^5 microorganisms per cm.^{3} of urine with repeated isolation of the same microorganism and no more than two species of microorganisms and patient has no fever (>38°c), urgency, frequency, dysuria, or suprapubic tenderness.

Definitions: Other infections of the urinary tract must meet at least one of the following criteria:

Criterion 1: Patient has organisms isolated from culture of fluid (other than urine) or tissue from affected site.

Criterion 2: Patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation, or during a histopathologic examination.

Criterion 3: Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38°c), localized pain, or localized tenderness at the involved site and at least one of the following:

a. purulent drainage from affected site.

b. organisms cultured from blood that are compatible with suspected site of infection.

c. radiographic evidence of infection, e.g., abnormal ultrasound, CT scan, magnetic resonance imaging (MRI), or radiolabel scan (gallium, technetium).

CDC/NHSN recommends the definitions of catheter-associated urinary tract Infection (CAUTI) as following statement: Catheter-associated urinary tract infection must meet one of the following criterion:

Criterion 1: Patient has had an indwelling urinary catheter within 7 days before the culture and has a positive urine culture, that is, $\geq 10^5$ microorganisms/ml of urine with no more than two species of microorganisms and Patient has no fever (>38°c), urgency, frequency, dysuria, or suprapubic tenderness.

Patient has had an indwelling urinary catheter within 7 days before the culture and at least one of the following:

1. One urine culture $\geq 10^5$ microorganisms/ml. of urine with no more than two species of microorganisms.

2. One positive urine culture with no more than two species identified and 10 wbc./hpf.

3. One positive urine culture with $\leq 10^5$ colonies/ml. of a single uropathogen in a patient currently on effective antibiotic treatment.

4. Physician diagnosis of hospital acquired UTI

Definition: Asymptomatic bacteriuria not catheter associated must meet at least one of the following criterion:

Criterion: Patient has not had an indwelling urinary catheter within 7 days before the first positive culture and has had at least two positive cultures, that is $\geq 10^5$ microorganisms/ml. of urine with repeated isolation of the same microorganisms and no more than two species of microorganisms and patient has no fever (>38°c), urgency, frequency, dysuria, or suprapubic tenderness.

2.2 Extended spectrum beta-lactamase - producing *E. coli*

2.2.1 Classification of Extended spectrum beta-lactamase-producing *E. coli*

Beta-lactams are the most utilized antibiotics for clinical treatment, high effectiveness, low cost and minimal side effects. They can inhibit bacterial cell wall synthesis (22). Production of beta-lactamases are the most common mechanism of resistance for the using of beta-lactam antibiotics in gram negative bacteria treatment (23). They are two scheme for classification beta-lactamase, molecular classification system and functional classification system (23).

The molecular classification divides beta-lactam into four major class, A to D. Class A, C and D enzymes are hydrolyze substrates by forming an acyl enzymes through a serine residue at their active site, but class B enzymes are metallo enzymes that utilize at least one active-site zinc ion to facilitate beta-lactam hydrolysis (23).

The functional classification devides beta-lactamases according to their hydrolytic and inhibition properties, four main groups (1-4) and multiple subgroups (a-f).

Group 1 cephalosporinases

The enzymes are cephalosporinases able to hydrolyze and resistance to Cephalosporins, Benzylpenicillin, Cephamycins. They are also resistant to inhibition by calvulanic acid (24).

Group 2 serine beta-lactamases

Subgroup 2 penicillinases are the largest groups of beta-lactamese. Enzymes in this group have been divided into many subgroups as follow:

Subgroup 2a penicillinases, a small group of beta-lactamases which have limited spectrum of hydrolytic activity. They can be inhibited by clavulanic acid and tazobactam. The majority of these enzymes are chromosomal encoded and predominant in gram positive cocci, including the staphylococci and occasionally enterococci (24).

Subgroup 2b beta-lactamases are able to hydrolyze Penicillin and early Cephalosporins, Cephaloridine and Cephalothin, they are strongly inhibited by clavulanic acid and tazobactam. The most common plasmid-mediaed beta-

lactamases are TEM-1, TEM-2, and SHV-1. At the present, 9 TEM and 29 SHV 2b were found in high prevalence among the Enterobacteriaceae prior to the introduction of broad spectrum Cephalosporins, Cefotaxime and Ceftazidime (24).

Subgroup 2be enzymes have hydrolytic against Penicillins and Cephalosporins of subgroup 2b beta-lactamases and one or more oxyimio beta-lactams, Cefotaxime, Ceftazidime, and Aztreonam. These ability are named extended-spectrum beta-lactamases or ESBLs.

Subgroup 2br enzymes are broad-spectrum beta-lactamases that resistant to clavulanic acid and related inhibitors subgroup 2b spectrum of activity (25).

Subgroup 2ber enzymes hydrolytic activity are similar subgroup 2bc beta-lactamases but resisitant to clavulanic acid inhibition.

Subgroup 2c enzymes are penicillinases that can hydrolyze Carbenicillin or Ticarcillin more than 60% as speedily as benzylpenicillin. They are easily inhibited by clavulanic acid or tazobactam.

Subgroup 2ce enzymes are a group of carbenicillinase with expanded activity against Cefepime and Cefpirome.

Subgroup 2d or oxacillinase family, their ability to hydrolyze Cloxacillin or Oxacillin. Many enzymes are the second largest family of beta-lactamase and high important, it is a causative factor for decreasing Carbapenem susceptibility in non-fermentative bacteria, Acenetobacter spp. and *P.aeruginosa* (25).

Subgroup 2de is a new group of ESBLs which in the oxacillinase family. These are able to hydrolyze Cloxacillin or Oxacillin and extended sprectrum include oxyimino but not Carbapenems.

Subgroup 2df is a new group of OXA enzymes which has Carbapenem-hydrolyzing ability. They are most frequently emerge in *A.baumanii.* However, plasmid-borne OXA-type enzymes, OXA-23, OXA-48 have been identified in the Enterobacteriaceae. These enzymes and their producing organisms are typically unresponsive to inhibition by clavulanic acid (25).

Subgroup 2e cephalosporinases can hydrolyze extended-spectrum Cephalospolins and inhibited by clavulanic acid or tazobactam (25).

Group 3 metallo-beta-lactamases (MBLs)

These group inhibited by metal ion chelators such as dipicolinic acid, ethylene diamine tetraacetic acid (EDTA), or 1, 10-0-phenanthroline. There were identified as chromosomal enzymes in gram positive or occasional gram negative bacilli, *Bacteroides fragilis, Stenotrophomonas maltophilia* (25).

Group 4 beta-lactamases

These enzymes remain to be incompletely characterized and need more information (25).

2.2.2 History and Epidemiology of ESBL-producing *E. coli*

ESBLs are enzymes that can hydrolyze a wide range of substrates, Penicillins, Monobactams and Cephalosporins with the exception of the Cephamycins (6). The resistance patterns are different in the both national and international level of epidemiology. Therefore it is important to know the incidence of ESBL-producing *E.coli* in the national group. The first beta-lactamase was described as a Penicillinase, can be hydrolyzed Penicillin in *E.coli* in 1940. In 1941, the plasmid-encoded Penicillin resistance spread rapidly in clinical isolates among *S.aureus* (26). In 1960s, the emergence of TEM-1 was ascribed in gram negative organisms, rising in Ampicillin resistance. The first report of an ESBL-producing organism in Germany and France in the 1980s was the structural mutants of the common penicillinases. Rising interests in spreading, constant evolution and resistances to the commonly used antibiotics showed evidence in 1990, including many reports from France, UK (27), Chile (28), Tunesia (29) and the USA (30). During 1990s there were also rising reports of genotypes of TEM and SHF derived ESBLs, particularly in association with the nosocomial outbreaks from many countries including the UK. The outbreaks were reported from the chronic care facilities (31), neonatology (32-34), neurosurgery (35), pedriatrics (36, 37), and obstetrics (38).

Over the last two decades, ESBLs have been detected most commonly in *K.pneumoniae* and *E.coli.* They have been implicated in numerous outbreaks of the nosocomial infection (39, 40). Since 2000, the survey from several European countries (including Spain, Italy, Greece, the UK and Canada) have shown an alarming trend of associated resistance to the antimicrobial agents among ESBLs producing organism

isolated from community (41-45). The resistance to Ciprofloxacin in Canada accounted for 66% of the isolates (45). These reports showed co-resistance to Co-trimoxazole, Tetracycline, Gentamicin and Ciprofloxacin. The reports from Israel and Spain have shown that ESBLs producing *E.coli* were important causes of community onset bloodstream infections (46, 47).

In Thailand 2000-2005, the Department of Medical Sciences, the Ministry of Public Health reported the prevalence of the extended spectrum beta-lactamase-producing *E.coli* to be regularly rising. During 2003 to 2005 the resistance rate to Ceftazidime in the reports by the screening test were 19%, 21% and 23%. While, those to Cefotaxime were 29%, 32% and 33% (48). The target sites namely the urine, blood and sputum had increasing rate of the extended spectrum beta-lactamase-producing *E.coli (48).*

Extended spectrum beta-lactamases (ESBLs) are enzymes produced by the non fermentative gram negative bacteria. Beta-lactamases are hydrolytic enzymes that break down the beta-lactam ring resulting in resistance to the beta-lactam antibiotics including the expanded spectrum Cephalosporins or third generation antibiotics such as Cefoxime, Ceftriazone, Ceftazidime and Monolactam e.g. Aztreonam. Extended spectrum beta-lactamase-producing *E. coli* (ESBL-producing *E.coli*) refers to bacteria in strains of *E.coli* producing enzyme beta-lactamase which induce resistance to antimicrobial agents such as aminoglycosides; Gentamicin or third generation Cephalosporins; Cefotaxime or Ciprofloxacin (6).

Epidemiology of ESBLs-producing *E. coli* in urinary tract nosocomial infection

ESBLs have been identified in the Enterobacteriaceae family especially *K.pneumoniae* and *E.coli* (4), also in non-fermentative gram-negative organisms, *P.aeruginosa* and *A.baummanii* (49). During the 1980s and 1990s, *K.pneumoniae* was mostly responsible for producing ESBLs. Since 2000, *E.coli* has emerged as an important organism responsible for producing ESBLs (49). The Study for Monitoring Antimicrobial Resistance Trends Program (SMART) has been ongoing monitors the activity of several antimicrobial agents against gram negative bacteria since 2002 in most regions of the world. The data from Asia-Pacific region showed the highest level

of antimicrobial resistance among the five global regions of the world. The prevalence of ESBLs in isolates show some increasing high rates of ESBL-producing *E.coli* more than 50% in some area in Asia. In Thailand during 2007, the rate as high as 50.8% were reported and a staggering 79% of *E.coli* collected in India were positive for ESBLs. The ESBLs prevalence in India was equally high among *E.coli* collected from the hospital and the community setting (50).

In the past, Enterobacteriaceae namely *K.pneumoniae* producing SHV and TEM types of ESBLs have traditionally been responsible for serious nosocomial infections until the end of the 1990s. At the present, this event has changed significantly, *E.coli* producing CTX-M beta-lactamases has emerged as an important cause of community-onset infections, mostly urinary tract infections (49). This infections are an important cause of invasive infections (51). The study from Spain, from January 1999 to December 2004, indicate that the number of urine culture processed from 11,936 to 16,128 ($p=0.014$) and the proportion of cultures with significant bacteriuria caused by *E.coli* and significant increase in proportion of ESBL-producing *E.coli* isolates from urine samples from 0.20% to 5.52%, $P<0.001$. The National Antimicrobial Resistance Surveillance Thailand (NARST) found that the incidence of ESBL-producing *E.coli* are a trend towards the increasing rate from 2000 to 2005 (48). The study in Thailand, found that in 2009, rates of ESBL-producing *E.coli* detected Cefotaxime screening were ranging from 20.8% to 69.3% (72). The study in Spain, found that in 2009, 23,839 urine samples were processed in the Microbiology Service of Rio Hortega University Hospital of which 4,522, *E.coli* was isolates in 60% (N=2,725), of which 6% (N=162) were ESBL-producing strains. In 2010, 30,438 cultures were processed of which 5062 were positive. *E.coli* was isolated in 59.4 (N=3007), of which 7% (N=210) were ESBL-producing *E.coli* (52).

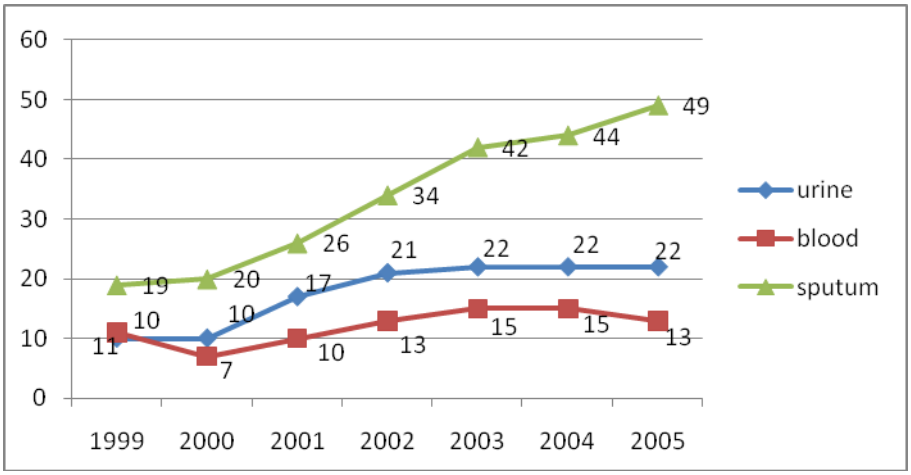


Figure 2.1 Prevalence of Extended spectrum beta-lactamases producing-*E.coli* in Thailand
Source: The National Antimicrobial Resistance Surveillance Thailand (NARST)

2.2.3 Antibiotic resistance of ESBL- producing *E.coli*

E. coli can spread both in the community and in the healthcare setting or nosocomial infection and has developed resistance to a number of antibiotics. It's the most commonly implicated and caused urinary tract infection for hospitalization (53, 54). The antimicrobial resistance varies in various countries commonly used the oral and parenteral antimicrobials including aminoglycosides, 3nd generation, Carbapenems Cephalosporins, and beta-lactam or beta-lactamase inhibitor combinations (55, 56). The mechanism of ESBL-producing *E.coli* consists in production of beta-lactamases, hydrolytic enzymes, with the ability to inactive antibiotics before they reach the penicillin-binding protein located at the cytoplasmic membrane (55, 56).

Common bacterial mechanism of antibiotic resistance can either chemically modify the antibiotic, and render it inactive through physical removal from the cell, or modify target site so that the antibiotic does not recognize it, the enzymatic inactivation of the antibiotic is the most common way. An existing cellular enzyme is modified to react with the antibiotic in such a way that it no longer affects the microorganism. An alternative strategy utilized by many bacteria is the alteration of the antibiotic target site. The change in genetic composition of bacterium confer that the drug effective is no longer active, resulting in drug resistance (57). The resistance to beta-lactams is mediated by a wide variety of beta-lactamases that can hydrolyze inactivate these drugs. Beta-lactamases can be either plasmid or chromosomally

mediated, and their expression can be constitutive or induced. Beta-lactamases of gram negative organisms are confined to the periplasmic space, which may explain some of the differences in their phenotypic expression and ease of laboratory detection.

2.2.4 Diagnosis and detections for ESBL-producing *E coli*

Laboratory diagnosis

The clinical laboratory is an early warning sign, alerting the medical to the new resistance mechanisms in clinical bacteria. There are two methods for detection of ESBLs, the first one is the phenotypic methods that use non-molecular techniques. This method detects the ability of these enzymes. ESBLs can hydrolyte different Cephalosporins. Another one is genotypic methods which is molecular techniques. These techniques detect the gene responsible for the production of the ESBL. The phenotypic methods are the most technique to clinical diagnosis because these tests are easy to do and cost effective (58).

Methods for ESBLs detection in ESBL-producing *E coli*

The clinical and laboratory standards institute (CLSI) has suggested three methods for detection ESBL production (59). There are screening, phenotypic confirmatory test and commercial available methods for ESBL producers.

Screening for ESBL producers

The one of the screening test for ESBL production by *K.pneumoniae, E.coli* and *Proteus mirabilis,* is using the disk diffusion methods for antibiotic susceptibility testing can screen for ESBL production by noting specific zone diameters which indicate a high level of suspicion for ESBL production (59). These agents: Cefpodoxime, Ceftazidime, Aztreonam, Cefotaxime, or Ceftrizone are used for screening improves the sensitivity of detection. The CLSI recommended a zone diameter of $\leq$22 mm. for a 10 microgram Cefpodoxime disk. Therefore, the CLSI recommends a change in Cefpodoxine screening breakpoint to $\leq$17 mm. (59). The second one for screening for ESBL production by *K.pneumoniae* and *E.coli* is dilution

antimicrobial susceptibility tests. Using of Ceftazidime, Cefotaxime, Ceftrizone or Aztreonam, at a screening concentration of 1$_{\mu}$g./ml (59). The growth at the screening antibiotic concentration, that is MIC of Cephalosporin of 2$_{\mu}$g./ml. is suspicious of ESBL production. It is an indication for the organism to be tested by a phenotypic confirmatory test (4).

Phenotypic confirmatory tests for ESBL production

The CLSI advocates two methods for confirmatory tests for ESBL-producing *E.coli* and *K.pneumoniae*. First, the Cephalosporin/Clavulanate combination disks, that uses of Cefotaxime 30$_{\mu}$g. or Ceftazidime disks 30$_{\mu}$g. with or without Clavulanate 10$_{\mu}$g. Disk for use in this method are available from several suppliers (Becton Dickison, Oxoid, and Mast). The recommendation from CLSI is prior to the combination disks becoming available, it was suggested that clavulanic acid solution be applied to the agar plates. The CLSI recommended that the disk test be performed with confluent growth on Mueller-Hinton agar, a difference of $\geq$5 mm. between the zone diameters of either of the Cephalosporin disk and their respective Cephalosporin/Clavulanate disk is taken to be phenotypic confirmation of ESBL production(60). The second, broth microdilution assays, these methods are using Ceftazidime $\geq$0.25 to 128$_{\mu}$g./ml., Ceftazidime plus Clavulanic acid 0.25/4 to 128/4$_{\mu}$g./ml., Cefotaxime 0.25 to 64$_{\mu}$g./ml.. The broth microdilution assays is a standard methods. The quality control is advocated that simultaneous testing with both non ESBL-producing organism and ESBL-producing organism. The implications of positive phenotypic confirmatory tests should be reported as resistant to all Cephalosporins and Aztreonam except Cephamycins, Cefoxitin and Cefotexan (60).

Commercially methods for ESBL detection

There are many commercial tools for laboratory diagnosis, including double disk, combination disc method and specific Etest. The Etest for ESBL detection is a plastic drug-impregnated strip, one of which contains a gradient of Ceftazidime (MIC test range 0.5 to 32$_{\mu}$g/ml.) and the other with Ceftazidime plus a constant concentration of Calvulanate 4$_{\mu}$g/ml., and now available the strips containing Cefotaxime and Cefotaxime/Clavulanate (15). Etest strips are useful for both

screening and phenotypic confirmation of ESBL-producing organism. The sensitivity of this method as a phenotypic confirmatory test is 87 to 100% and the specificity is 95% to 100% (59).

2.2.5 Antimicrobial treatment for ESBL-producing organisms

The antimicrobial treatment of hydrolyzing the beta-lactam ring found in Penicillin, Cephalosporins and Aztreonam except Cephamycins often have other mechanisms that confer resistance to the classed of antimicrobials. The empirical antibiotic choices should be individual basing on institutional antibiograms, that are different from hospital to hospital, from city to city, and from country to country (4).

The Clinical Laboratory Standard Institute (CLSI) recommended that ESBL-producing *E.coli* should be reported as a resistant to Penicillins, Cephalosporins and Aztreonam unrelatedly of in vitro susceptibility data. The level of antibiotics resistant in vitro conferred by the presense of ESBL to beta-lactam/beta-lactamase inhibitor combinations is variable (60).

Beta-lactams/Beta-lactamase inhibitor combination

Tazobactam has been found to be more potent compared with clavunic acid against certain CTX-M type ESBL. The available clinical evidence regarding the utility of beta-lactams/beta-lactamase inhibitor combination for treatment of ESBL is rather limited. In some study, the patient outcomes have been related to Piperacillin/ Tazobactam treatment.

Cephalosporins use

In clinical trial, the success rate were similar in seven patients with CTX-M producing *E.coli* treated with Ceftazidime compared with eight patients that treated with Imipenem (86% compared with 88%) (4). The most experts dispute against the using of Cephalosporin for the treatment of choice for ESBL-producing *E.coli*.

Cephamycin use

The Cephamycin including Cefoxitin and Cefotexan are general to use (4). There are some reports of the use of Cephamycins in the treatment of ESBL-

producing oranisms. One of these study, selection of porin resistant mutants occurred during therapy, resulting in Cefoxitin resistance and relapse of infection. However, there is a general reluctance to use because of it may decrease the expression of outer membrane proteins, then creasing resistance to these drug during therapy

Carbapenems use

Carbapenems are the antibiotic of choice and against the infections caused by ESBL. The major drugs in this class are Imipenem, Meropenem and Ertapenem, these have become widely recognized as the first choice for treatment of ESBL-producing *E.coi*. These drugs are highly stable to hydrolysis by ESBL and distributed the high concentrations into the tissue and there is no inoculums effect (4).

2.3 Related literatures

There are many studies have used a case-control study and cohort study to find risk factors, the results were conflicted due to the differences in study population, method of selection cases and controls and sample size.

Gender

Apisanthanarak et.al. found that the proportion of female patients were higher than male (72% vs 28%) (4). Y.S Yang, et al. found that the proportion of male patients were higher in the ESBL group than the non ESBL group (66.7% vs. 23.9%; p=0.005) (61).

Prior antibiotics used within last year and Cephalosporin used within last year

In addition, using of heavy antibiotic is a risk factor that has the relationship between third generation, Cephalosporin, and acquirement of ESBL producing gram negative bacteria (62). Furthermore, the antibiotics exposure in last month and inpatient use of urinary catheter were found the significant association with ESBL producing organisms (63). Using of variety of antibiotics classes include Quinolones, Trimethoprim-Sulfamethoxazole, Aminoglycosides and Metronidazole

has been found to be associated with infections too (63). Goyal, K.N et.al found that the used of antibiotic in last 1 month was a risk factor for ESBL infection (OR=3.154, 95%CI; 1.727-5.761, p<0.001) (63). Kruter S.P. et.al. found that antibiotic therapy within the year was a risk factors for ESBL-producing strain infection (OR=3.03, 95%CI; 1.33-7.68, p=0.006) (64). Apisarnthanarak et.al found that the previous using antibiotics, especially to third-generation Cephalosporins and Fluoroquinolones were the risk factors for community onset ESBL-producing *E.coli* infection (4). Chaiwarith, R., et al. found that prior exposure to Cephalosporins (OR=3.92, 95%CI; 2.72-6.77) (67).

Urine catheter used within 30 days

Mansouri M, et al. found that the use of catheter was the risk factor for ESBL-producing *E.coli* (OR= 6.28, 95%CI; 1.86-21.02, p<0.001) (62). Goyal et al. found that the use of urinary catheter was a risk factor for ESBL infection (OR=4.28, 95%CI; 2.21-8.29, p<0.001) (63). Yang Y.S., et al. found that the patients in the ESBL group with indwelling urinary catheters had statistically significance association (41.7% vs 6.5%; p=0.002) (61).

Previous hospitalization

Kuster SP., et.al. found that prior hospitalization did not enhance the risk factor for infection (64). Van der Starre WE., et al. found that hospitalization in the past 6 month was an acquisition risk factors for that infection (OR=2.28, 95%CI; 1.17-4.44, p 0.013) (66). Briongos–Figuero L.S, et al. found that hospitalization in previous month did not enhance the risk factor for infection (52).

ICU stay

ICU stay was an acquisition risk factors for that infection (OR=2.55, 95%CI; 1.10-5.90) (64). Kuster et.al. found that urinary catheter used, diabetes, malignoma and co-morbidities were not associated with increasing risk (64). Goyal et al. found that an admission in intensive care unit was not associated with urinary tract infection (OR=2.16 95% CI; 0.98-4.73) (63). Yang YS, et al. found that the patients in ESBL group had statistical significance more patients with prior ICU admissions (41.7% vs 4.4%; p=0.003) than the non-ESBL group (61).

Invasive urine catheter

Briongos-Figuero L.S, et al. found that the patients who indwelling urinary catheter did not enhance the risk factor for infection (52).

Chronic renal failure

Willize E et al. found that urinary tract disorder was an acquisition risk factors for that infection (OR=2.30, 95%CI; 1.21-4.35, p=0.009 (68). Briongos L.S et al. found that CRF did not enhance the risk factor for infection (52).

Diabetic mellitus

Goyal et al. found that diabetes mellitus was not associated with urinary tract infection (OR=1.12 95%CI; 0.51-2.47) (63). Pena et.al. found that diabetes mellitus was not associated with urinary tract infection (p-value<0.001) (5). Briongos-Figuero L.S et al. found that Diabetes mellitus did not enhance the risk factor for infection.

Recurrent UTI

Willize E et al. found that recurrent UTI was a acquisition risk factors for that infection (OR=2.24 95%CI; 1.22-4.10, p=0.008) (66). Briongos L.S et al. found that recurrent UTI did not enhance the risk factor for infection (p=0.032) (52).

CHAPTER III
MATERIALS AND METHODS

3.1 Research Design

Retrospective cohort study was conducted to indentify incidence and risk factors associated with ESBL-producing *E.coli* among inpatients with nosocomial urinary tract infection at Taksin hospital, Bangkok Metropolitan Administration by using retrospectively reviewing hospital records of patients who admitted during the year 2011.

3.2 Study Population

Patients who were admitted at Taksin Hospital, Bangkok Metropolitan Administration during January 1, 2011 through December 31, 2011 and had urine culture positive. The patients who satisfied the following criteria.

Inclusion criteria

1. Patients who had admitted in hospital for more than 48 hours.
2. Patients who admitted in the departments of medicine (male), medicine (female), surgery (male), surgery (female), gynecology and obstetrics, ICU, stroke unit, private floor 14-16, orthopedics (male) and orthopedics (female).
3. Patients who had sign of urinary tract infection and had the urine culture positive after 48 hour of admission at the first time in this hospital.

Exclusion criteria

1. Patients who had community acquired infection with ESBL-producing *E.coli* by having urinary tract infection before 48 hours.
2. Patients who had incomplete data for analysis.

A total of 937 patients were included in the analysis. Total 197 patients had culture positive with *E.coli,* 83 patients had ESBL-producing *E.coli* and 114 patients had non ESBL-producing *E.coli* (Figure 3.1).

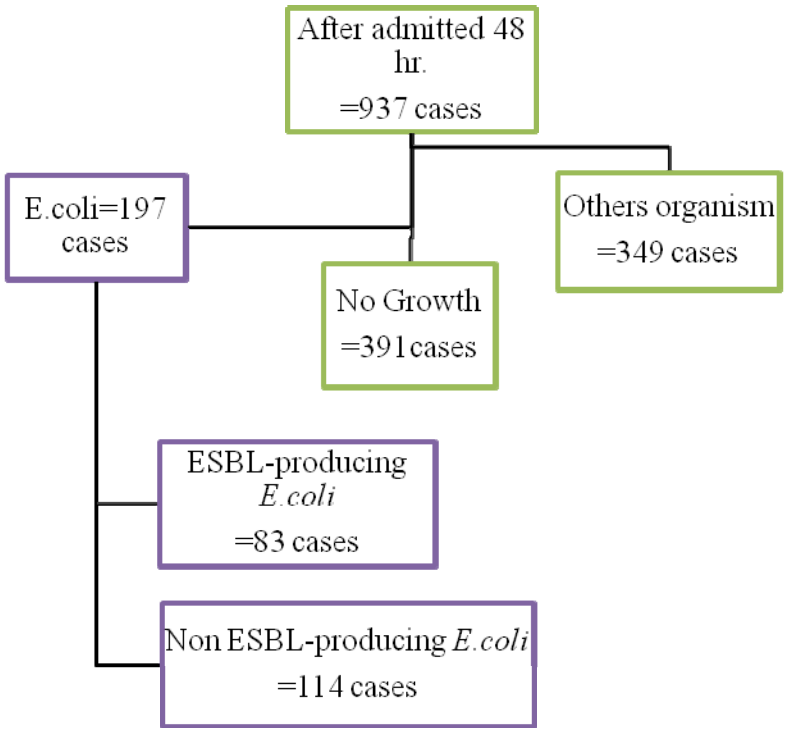


Figure 3.1 Study Population Diagram

3.3 Sample Size and Sample Selection

The sample size was calculated by the following formula (67);

$$n_1 = \frac{(Z_\alpha + Z_\beta)^2 \times \overline{PQ} \times (r+1)}{(P_1 - P_0)^2 \times r}$$

$$\overline{P} = \frac{P_1 + rP_0}{1+r}$$

$$r = \frac{n_0}{n_1}$$

$$\overline{Q} = 1 - \overline{P}$$

n_1 = The number of sample who had urinary tract infection by ESBL-producing *E.coli.*

n_2 = The number of sample who had urinary tract infection by non ESBL-producing *E.coli.*

r = Ratio of non exposed and exposed = 1 : 1

P_1 = The proportion of patients who exposed to prior antibiotic used and had urinary tract infection by ESBL-producing *E.coli* (63).= 0.75

P_0 = The proportion of patients who did not expose to prior antibiotic used and had urinary tract infection by ESBL-producing *E.coli* (63). = 0.49

Z_α = Z value from table standard normal distribution at the specific level of alpha = 1.96

Z_β = Z value from table standard normal distribution at the specific level of beta = 0.84

From the original article "Extended spectrum beta-lactamases in *Escherichia coli* & *Klebseilla pneumoniae* & associated risk factors" (63).

Computation of sample size;

$$n_1 = \frac{(1.96+0.84)^2 \times 0.62 \times 0.38 \times 2}{(0.75-0.49)^2 \times 1}$$

$n_1 = 52.7$

Therefore, this study included minimum sample size of 53 for exposed group with prior antibiotic used and 53 for comparison group. The total number of patients in this study who had exposed to prior antibiotic used were the expose group, and had not exposed to prior antibiotic used as the comparison group, they were 384 and 553 cases respectively.

3.4 Research Tools

Data was retrieved from medical records using data collection form prepared by the investigator. It's consisted of;

1. General characteristics; gender, age, department admitted, principle diagnosis for present admission and antibiotic used during this admission.

2. The clinical characteristics risk factors; prior antibiotics used within last year, urine catheter used within 30 days, recurrent urinary tract infection, previous hospitalization, ICU stay during present admission, patient's co-morbidity and antibiotic used during this admission.

3. The co-morbidity of total study population

4. Overall incidence density and incidence density of ESBL-producing *E.coli* nosocomial urinary tract infection among factors.

5. Comparison of median survival time of ESBL-producing *E.coli* nosocomial urinary tract infection among factors.

6. Crude analysis of associations between factors and ESBL-producing *E.coli* nosocomial urinary tract infection.

7. Multivariated analysis of association between the risk factors and ESBL-producing *E.coli* nosocomial urinary tract infection

8. Antimicrobial susceptibility of ESBL-producing *E.coli* infection.

3.5 Method of Data Collection

3.5.1 This research were submitted and approved by ethical committee of Faculty of Public Health, Mahidol University and Taksin Hospital, Bangkok Metropolitan Administration.

3.5.2 Permission from directors of Taksin Hospital was asked.

3.5.3 Data was retrieved from the inpatients record and laboratory reports of study population in Taksin Hospital, Bangkok Metropolitan Administration.

3.6 Statistical Analysis

The data were statistically analyzed by using Statistical Package for the Social Science (SPSS) with the significance level at p-value ≤0.05.

3.6.1 Descriptive statistics: frequency, percentage, mean, standard deviation to describe characteristic of study population

3.6.2 Analytic statistics:

1) Univariate analysis

a. Kaplan-Meier was used to demonstrate survival graphs of the ESBL- producing *E.coli* infection among categories of each factor.

b. The log-rank test was used to demonstrate significant differences of ESBL- producing *E.coli* infection among categories of each factors.

2) Multivariate analysis

Cox's regression was used to demonstrate crude and adjusted association between ESBL-producing *E.coli* and risk factors by hazard ratio (HR) with 95% CI and p-value.

3.7 Ethic Issue

The research was reviewed and approved according to the Standard Operating Procedures of Ethical Review Committee for Human Research, Faculty of Public Health, Mahidol University.

CHAPTER IV
RESULTS

This retrospective cohort study was carried out among inpatients with urinary tract infection after admission for more than 48 hours at Taksin hospital, Bangkok Metropolitan Administration. It aimed to determine incidence density and factors associated with extended spectrum beta-lactamases-producing *E.coli* nosocomial infection. Data was retrieved from the medical records of inpatients admitted during the year 2011 among total 2,603 patients who had urinary tract infection with positive urine culture. These groups of population consisted of 1,776 inpatients and 827 outpatients. Of those 1,776 inpatients, only 937 patients were considered to be studied population who had nosocomial urinary tract infection due to infection occurred after 48 hours of admission. However, total study population included in the analysis was 937. Out of 937 patients, there were 83 patients were positive on ESBL-producing *E.coli* and 114 patients were positive with non ESBL-producing *E.coli*. The length of stay in hospital in this study ranging from 2 days to 398 days (56.9 weeks) with the average of 29.52 days. With to total number of new cases of 83, the overall incidence density of ESBL-producing *E.coli* infection was 5.1 per 100 person-weeks and the total person-weeks of study population was 1,644 weeks.

However, most of previous investigations mostly reported prevalence instead of incidence. Which prevalence includes both new and old cases, so it could not forecast the evidence of new group of patients in these study hospital. So term of incidence density and this retrospective cohort design would further provide substantial data for epidemiological need. The results were presented as follows:

4.1 General characteristics of study population; gender, age, department admitted and principle diagnosis

4.2 Clinical characteristics of study population; prior antibiotics used within last year, urine catheter used within 30 days, recurrent urinary tract infections,

previous hospitalization, ICU stay during present admission, patient's co-morbidity, invasive urine catheter used during present admission and antibiotic used in this admission

4.3 The co-morbidity of study population

4.4 Overall incidence density and incidence density of ESBL-producing *E.coli* nosocomial urinary tract infection among factors

4.5 Comparison of median survival time of ESBL-producing *E.coli* nosocomial urinary tract infection among factors

4.6 Crude analysis associations between risk factors and ESBL-producing *E.coli* nosocomial urinary tract infection

4.7 Multivariate analysis associations between risk factors and ESBL-producing *E.coli* nosocomial urinary tract infection

4.8 Antimicrobial susceptibility of ESBL-producing *E.coli* infection

4.1 General characteristics of study population; gender, age, department admitted and principle diagnosis

Among total study population of 937, there were 54.4% females and 45.6% were males. With mean of age 56.9±23.5 years, the majority of study population (36.4%) aged between 56-75 years. While aged 76-95 years group was 23.1 percent, less than 35 years age group was 21.6 percent, 36-55 years age group was 18.1 percent and over 95 years was 0.9 percent. By departments of admission, about 65.3 percent of study population were from medical ward, 11.8 percent were from surgical ward, 11.3 percent were from ob-gyn ward, 11.5 percent were from intensive care unit. The results from urine culture showed no growth for 41.8 percent, other organisms for 37.1 percent, *E.coli* for 12.2 percent and ESBL-producing *E.coli* for 8.9 percent. The majority of principle diagnosis were others diagnosis for 78.8 percent, diabetic mellitus and renal disease in 6.5 percent, urinary tract infection in 5.9 percent, heart disease in 3.2 percent, hypertension in 3.1 percent, sepsis in 1.5 percent, malignant 0.4 percent and other diagnosis in 78.8 percent (Table 4.1).

Table 4.1 General characteristics of total study population

Variable	Number (N=937)	Percentage
Gender		
Male	427	45.6
Female	510	54.4
Age (year)		
≤ 35	202	21.6
36-55	170	18.1
56-75	341	36.4
76-95	216	23.1
>95	8	0.9
Mean of age 56.9 ±23.5 years		
Department		
Medical ward	612	65.3
Surgical ward	111	11.8
Intensive care unit	108	11.5
Ob-gyn ward	106	11.3
Results of urine culture		
E.coli	114	12.2
ESBL-producing *E.coli*	83	8.9
Others organism	348	37.1
No growth	392	41.8
Principle diagnosis		
Diabetes mellitus	61	6.5
Hypertension	29	3.1
Renal disease	61	6.5
Heart disease	30	3.2
UTI	55	5.9
Sepsis	14	1.5
Malignancy disease	4	0.4
Others diagnosis	738	78.8

4.2 Clinical characteristics of study population

During the year before admission, majority of study population did not received antibiotic (59.0%), and had no previous hospitalization (77.1%). In this admission, most of them did not stay in ICU (95.1%), did not use the urine catheter within 30 days (82.1%). During this admission, most of them neither had no recurrent urinary tract infections (94.2%), and 43.3 of them received Cephalosporin group, used other antibiotic in 7.7 %, and did not use antibiotic in 49.0 percent. The majority of study population did not have co-morbidity (44.9%) and 10.8 percent had other co-morbidity (Table 4.2).

Table 4.2 Clinical characteristics of study population

Variable	Number (N=937)	Percentage
Prior antibiotics used within last year		
Yes	384	41.0
No	553	59.0
Previous hospitalization		
Yes	215	22.9
No	722	77.1
ICU stay during present admission		
ICU stay	46	4.9
Non ICU stay	891	95.1
Urine catheter used within 30 days		
Yes	168	17.9
No	769	82.1
Antibiotic used in this admission		
Cephalosporin group	406	43.3
Other antibiotics	72	7.7
No use antibiotic	459	49.0
Recurrent urinary tract infection		
Yes	54	5.8
No	883	94.2

Table 4.2 Clinical characteristics of study population (cont.)

Variable	Number (N=937)	Percentage
Invasive urine catheter		
Yes	314	33.5
No	623	66.5
Co-morbidity		
Yes	516	55.1
No	421	44.9

4.3 The co-morbidity of study population

It was found that patients in this group had diseases of co-morbidity. They were diabetes mellitus (17.6%), hypertension (17.6%), renal disease (9.8%), malignancy disease (1.5%), heart disease (9.1%), and septicemia (7.3%) (Table 4.3).

Table 4.3 Co-morbidity factor of study population

Variable	Number (N=937)	Percentage
Diabetes mellitus		
Yes	165	17.6
No	772	82.4
Hypertension		
Yes	165	17.6
No	772	82.4
Renal disease		
Yes	92	9.8
No	845	90.2
Malignancy disease		
Yes	14	1.5
No	923	98.5

Table 4.3 Co-morbidity factor of study population (cont.)

Variable	Number (N=937)	Percentage
Heart disease		
Yes	85	9.1
No	852	90.9
Septicemia		
Yes	68	7.3
No	869	92.7

4.4 Overall incidence density and incidence density of ESBL-producing *E.coli* nosocomial urinary tract infection among factors

Among 937 patients, the total follow up person-weeks of study population was 1,644 weeks minimum, there were 83 cases of ESBL-producing *E.coli*. Overall incidence density of ESBL-producing *E.coli* infection was 5.1 per 100 person weeks. The incidence density of ESBL-producing *E.coli* infection among female was higher than male (6.7 vs. 3.0 per 100 person-week). By age group, incidence density of ESBL-producing *E.coli* infection was 6.4 per 100 person-weeks in study population with age group 56 years or over, 2.7 per 100 person-weeks in study population with age group under 56 years. By department admitted, incidence density of ESBL-producing *E.coli* infection was 8.1 per 100 person-weeks in study population with admitted in intensive care unit, incidence density of ESBL-producing *E.coli* infection was 6.3 per 100 person-weeks in study population with admitted in ob-gyn ward, incidence density of ESBL-producing *E.coli* infection was 5.0 per 100 person-weeks in study population with admitted in medical ward and incidence density of ESBL-producing *E.coli* infection was 1.9 per 100 person-weeks in study population with admitted in surgical ward. It was found that incidence density of ESBL-producing *E.coli* with chronic disease was higher than those other diagnosis and infection disease (18.3 vs.3.5 and 2.5 per 100 person-weeks). By antibiotic used in this admission, incidence density of ESBL-producing *E.coli* infection was 35.8 per 100 person-weeks in study population with used other antibiotic was higher than those used

Cephalosporin group and no used antibiotic (35.8 vs. 3.0 and 0.4 per 100 person-weeks). The incidence density of ESBL-producing *E.coli* of study population who had co-morbidity was 6.0 per 100 person-weeks which was higher than who had no co-morbidity was in 3.8 per 100 person-weeks (Table 4.4).

By the risk factors, the incidence density of ESBL-producing *E.coli* of study population who used antibiotic prior to the admission within last year was 9.4 per 100 person-weeks which was higher than those who never used antibiotics prior to the admission within last year in 1.4 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who never previous hospitalization was 5.5 per 100 person weeks which was higher than those who had previous hospitalization in 3.9 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who had never admitted in ICU during present admission was 5.4 per 100 person-weeks which was higher than those who had admitted in ICU during present admission in 0.8 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who used urine catheter within 30 days was 11.4 per 100 person weeks which was higher than who never used urine catheter within 30 days was in 2.9 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who had recurrent urinary tract infection was 7.2 per 100 person-weeks which was higher than who had no recurrent urinary tract infection was in 4.8 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who had invasive urine catheter was 7.8 per 100 person-weeks which was higher than those who never had invasive urine catheter was in 3.6 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who had no diabetic mellitus was 2.1 per 100 person-weeks which was higher than those who had diabetic mellitus was in 2.0 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who had hypertension was 6.0 per 100 person-weeks which was higher than who never had hypertension was in 4.8 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who never had renal disease was 2.1 per 100 person-weeks which was higher than who had renal disease was in 1.5 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who had malignancy diseases was 3.6 per 100 person-weeks which was higher than those who

never had malignancy diseases was in 2.0 per 100 person week. The incidence density of ESBL-producing *E.coli* of study population who had heart diseases was 2.40 per 100 person-weeks which was higher than those who never had heart diseases was in 2.0 per 100 person-weeks. The incidence density of ESBL-producing *E.coli* of study population who never had septicemia was 2.1 per 100 person-weeks which was higher than those who had septicemia was in 1.0 per 100 person-weeks. (Table 4.4)

Table 4.4 Incidence density of ESBL-producing *E.coli* by risk factors

Variables	Total	Number of ESBL-producing *E.coli*	Person-weeks	Incidence density (per100 person-weeks)
Overall	937	83	1644	5.1
Gender				
Male	427	22	736	3.0
Female	510	61	908	6.7
Age (year)				
≤ 55	372	16	599	2.7
≥ 56	565	67	1045	6.4
Department				
Medical ward	612	54	1090	5.0
Surgical ward	111	4	207	1.9
Intensive care unit	108	14	175	8.1
Ob-gyn ward	106	11	172	6.3
Principle diagnosis				
Infection disease	69	33	1302	2.5
Chronic disease	126	47	257	18.3
Other diagnosis	742	3	85	3.5
Antibiotic used in this admission				
Cephalosporin group	406	22	739	3.0
Other antibiotic	72	58	162	35.8
No use antibiotic	459	3	743	0.4

Table 4.4 Incidence density of ESBL-producing *E.coli* by risk factors (cont.)

Variables	Total	Number of ESBL-producing *E.coli*	Person-weeks	Incidence density (per100 person-weeks)
Co-morbidity				
Yes	516	43	778	5.5
No	421	27	713	3.8
Prior antibiotics used within last year				
Yes	384	71	757	9.4
No	553	12	887	1.4
Previous hospitalization				
Yes	215	19	483	3.9
No	722	64	1161	5.5
ICU stay during present admission				
ICU stay	46	1	122	0.8
Non ICU stay	891	82	1522	5.4
Urine catheter used within 30 days				
Yes	168	48	421	11.4
No	769	35	1223	2.9
Recurrent urinary tract infection				
Yes	54	10	138	7.2
No	883	73	1506	4.8
Invasive urine catheter				
Yes	314	44	565	7.8
No	623	39	1079	3.6
Diabetes mellitus				
Yes	165	7	351	2.0
No	772	27	1293	2.1
Hypertension				
Yes	165	21	351	6.0
No	772	62	1293	4.8

Table 4.4 Incidence density of ESBL-producing *E.coli* by risk factors (cont.)

Variables	Total	Number of ESBL-producing *E.coli*	Person-weeks	Incidence density (per100 person-weeks)
Renal disease				
Yes	92	3	198	1.5
No	845	31	1446	2.1
Malignancy disease				
Yes	14	1	28	3.6
No	923	33	1616	2.0
Heart disease				
Yes	85	3	125	2.4
No	852	31	1519	2.0
Septicemia				
Yes	68	1	100	1.0
No	869	33	1544	2.1

4.5 Comparison of median survival time ESBL-producing *E.coli* nosocomial urinary tract infection and among factors

Kaplan-Meier test was used to construct survival curve or function and Log-rank test was used to compare the equivalence of two or more survival curves or function for each categories of factor by p-value.

Overall incidence

Overall incidence density among this group of study population was 5.1 per 100 person-weeks. The median survival times for overall were 181 weeks. Survival rates for 4, 6, 8 and 16 weeks of follow up on urinary tract infection for 82.0%, 72.7%, 56.6%, and 37.6%, respectively.

The factors, gender, age, principle diagnosis, antibiotic used during present admission, antibiotics used within last year, ICU stay during present admission, urine

catheter used within 30 days, having co-morbidity and invasive urine catheter in this admission were different with survival time. (Figure 4.1)

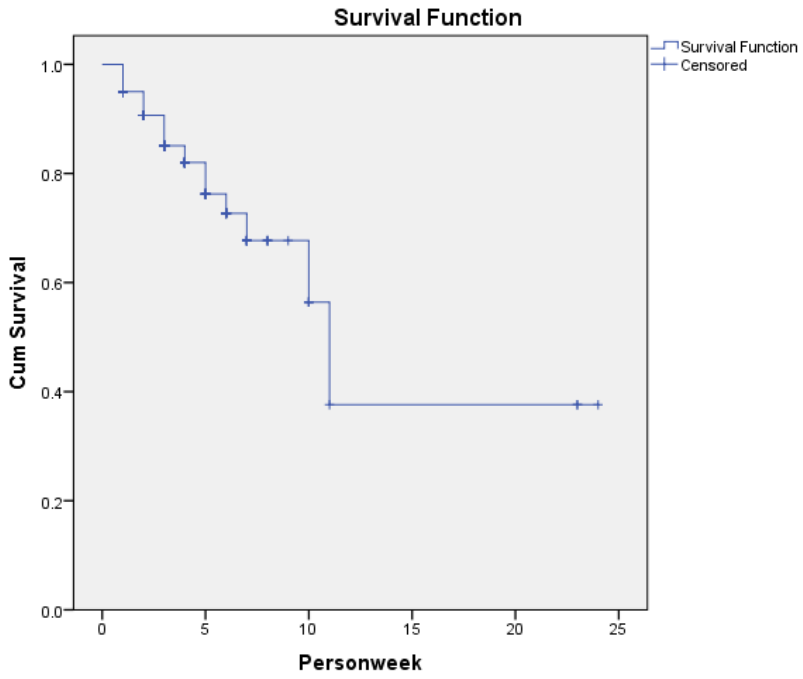


Figure 4.1 Overall survival curves of nosocomial urinary tract infection by ESBL-producing *E.coli*

Gender

Female patients had higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among male patients significantly, which were 6.7 and 3.0 per 100 person-weeks, respectively (Figure 4.2).

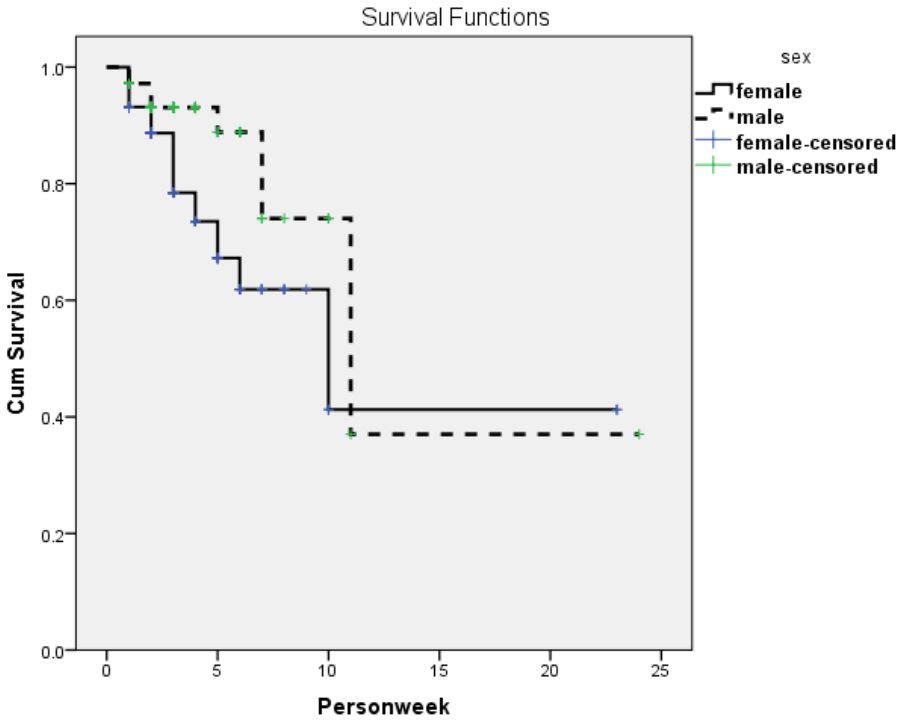


Figure 4.2 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by gender (p <0.001)

Age

Patients with age group ≥56 years had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among age group ≤ 55 years significantly, which were 6.4 and 2.7 per 100 person-weeks, respectively (Figure 4.3).

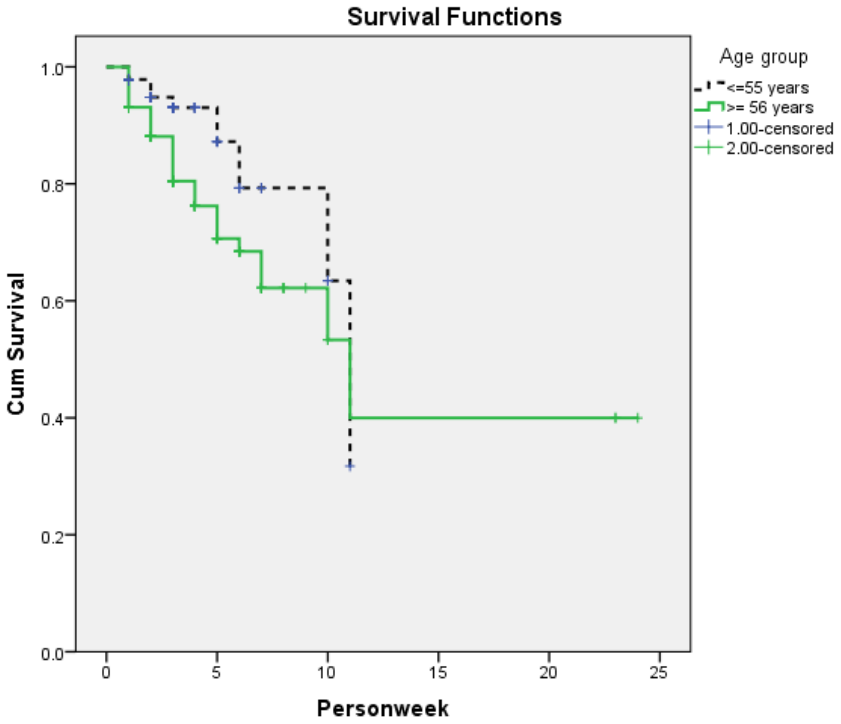


Figure 4.3 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by age group (p <0.001)

Principle diagnosis

Patients with chronic disease had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients with others diagnosis and infectious disease significantly, which were 18.3 vs 3.5 and 2.5 per 100 person-weeks, respectively (Figure 4.4).

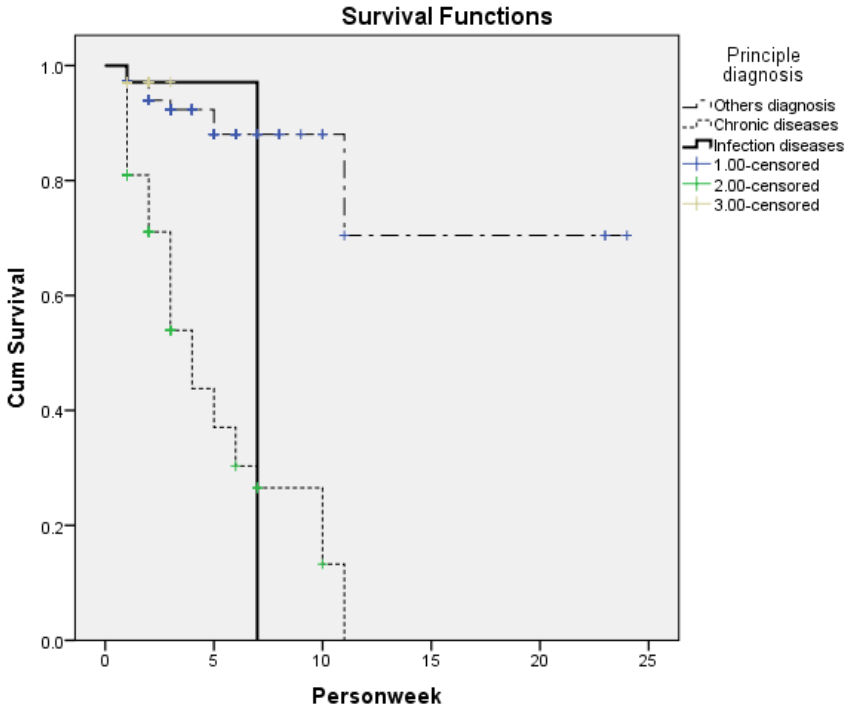


Figure 4.4 Comparison of survival curves of nosocomial urinary tract infection with by ESBL-producing *E.coli* by principle diagnosis (p <0.001)

Admitted department

Patients admitted in intensive care unit had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients admitted in ob-gyn ward, medical ward and surgical ward significantly, which were 8.1vs. 6.3, 5.0 and 1.9 per 100 person-weeks, respectively (Figure 4.5).

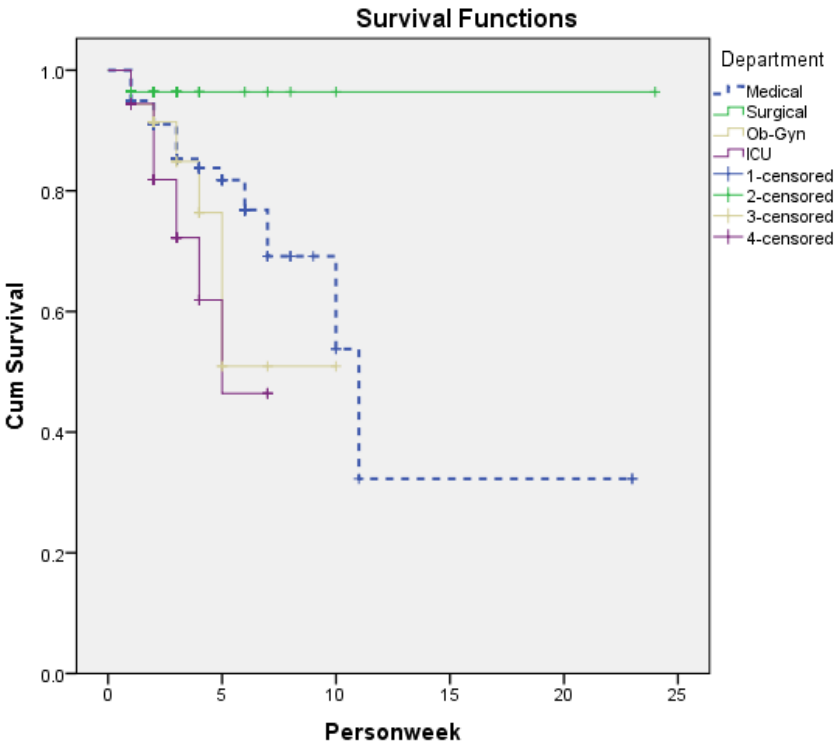


Figure 4.5 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by Department (p =0.047)

Antibiotic used in this admission

Patients with other antibiotics used in this admission had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients with used cephalosporin group and no used antibiotic significantly, which were 35.8 vs 3.0 and 0.4 per 100 person-weeks, respectively (Figure 4.6).

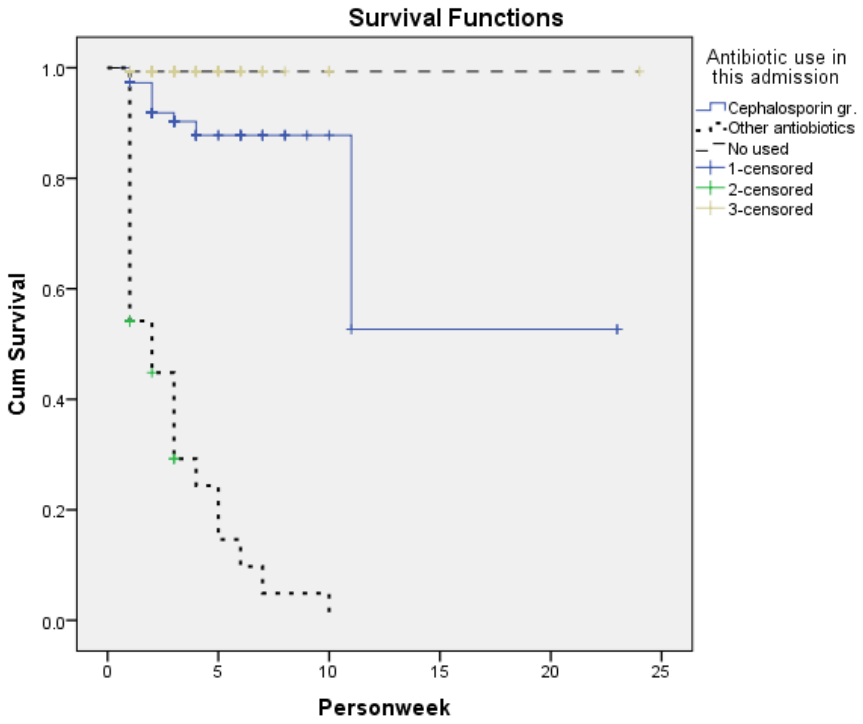


Figure 4.6 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by antibiotic used in this admission. (p <0.001)

Prior antibiotic used within last year

Patients with prior antibiotics used within last year had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients with never prior antibiotics used significantly, which were 9.4 and 1.4 per 100 person-weeks, respectively (Figure 4.7).

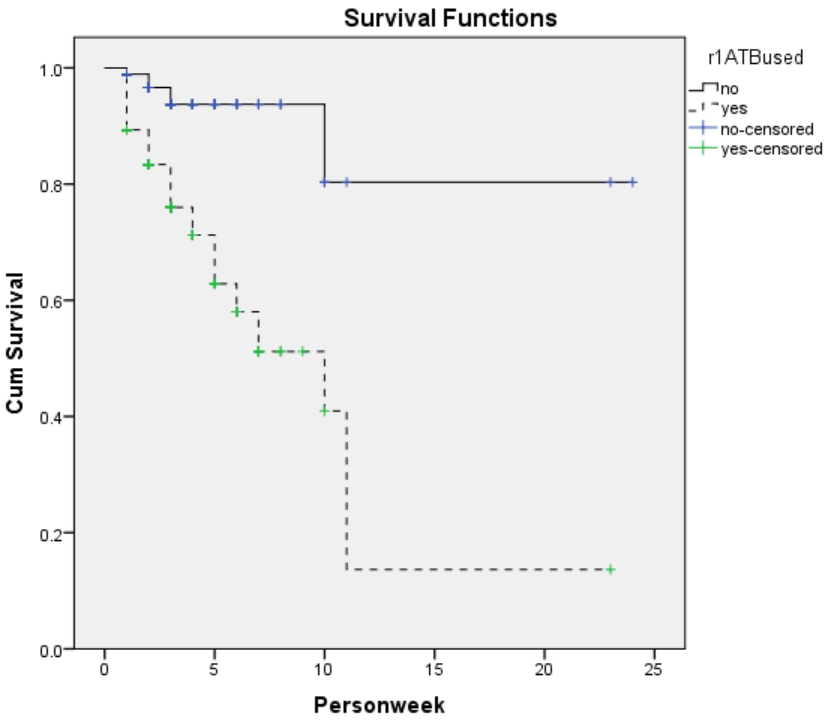


Figure 4.7 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by prior antibiotic used within last year. (p <0.001)

Previous hospitalization

Patients with no history previous hospitalization had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients with previous hospitalization significantly, which were 5.5 and 3.9 per 100 person-weeks, respectively (Figure 4.8).

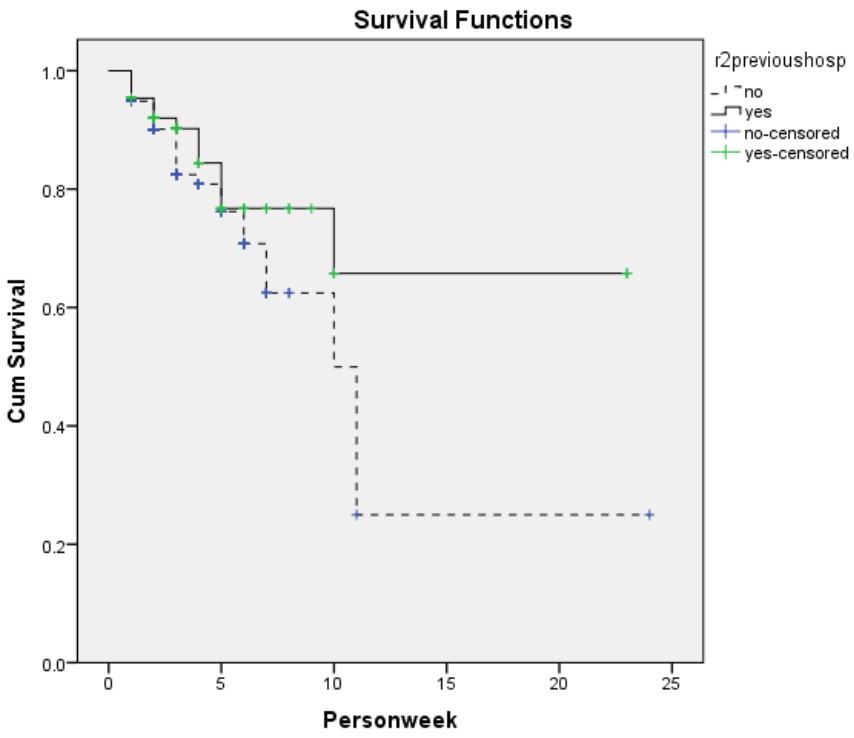


Figure 4.8 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by previous hospitalization. (p=0.128)

ICU stay during present admission

Patients with no history of admission in ICU during present admission had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients with admitted in ICU during present admission significantly, which were 5.4 and 0.8 per 100 person-weeks, respectively (Figure 4.9).

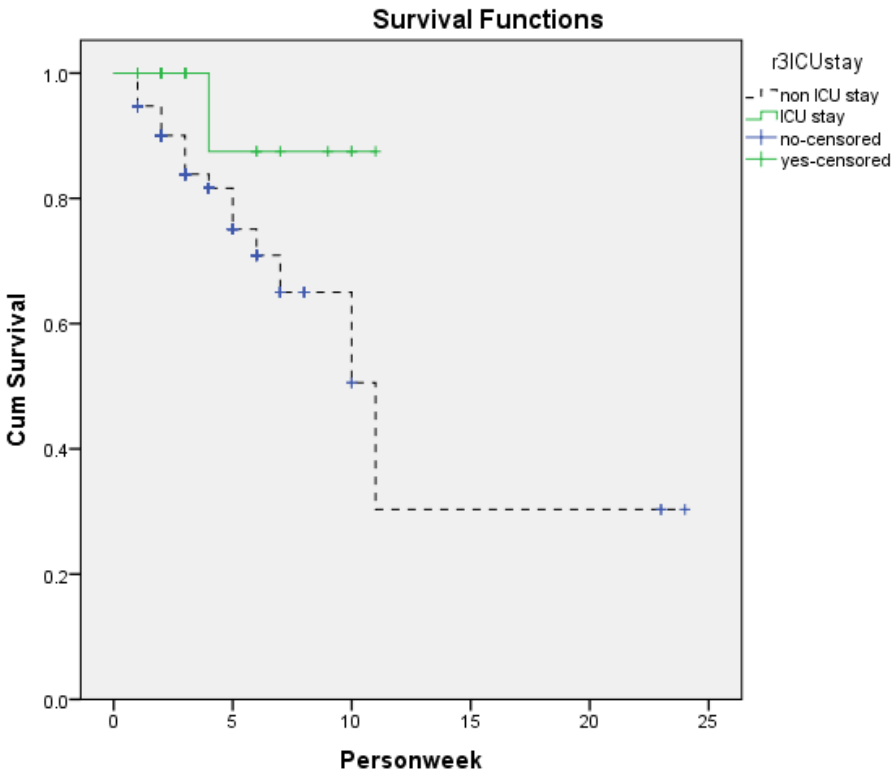


Figure 4.9 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by ICU stay during present admission. (p =0.019)

Urine catheter used within 30 days

Patients with urine catheter used within 30 days had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients with never used urine catheter within 30 days significantly, which were 11.4 and 2.9 per 100 person-weeks, respectively (Figure 4.10).

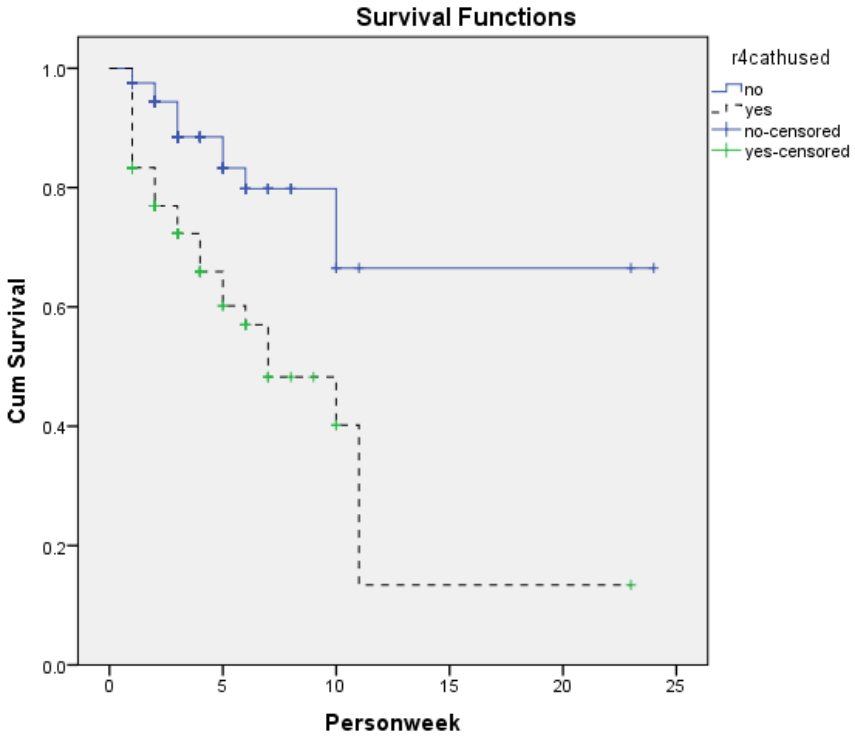


Figure 4.10 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by urine catheter used within 30 days. ($p < 0.001$)

Recurrent urinary tract infection

Patients with recurrent urinary tract infection had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients with nonrecurrent urinary tract infection, which were 7.2 and 4.8 per 100 person-weeks, respectively, with no significant difference (Figure 4.11).

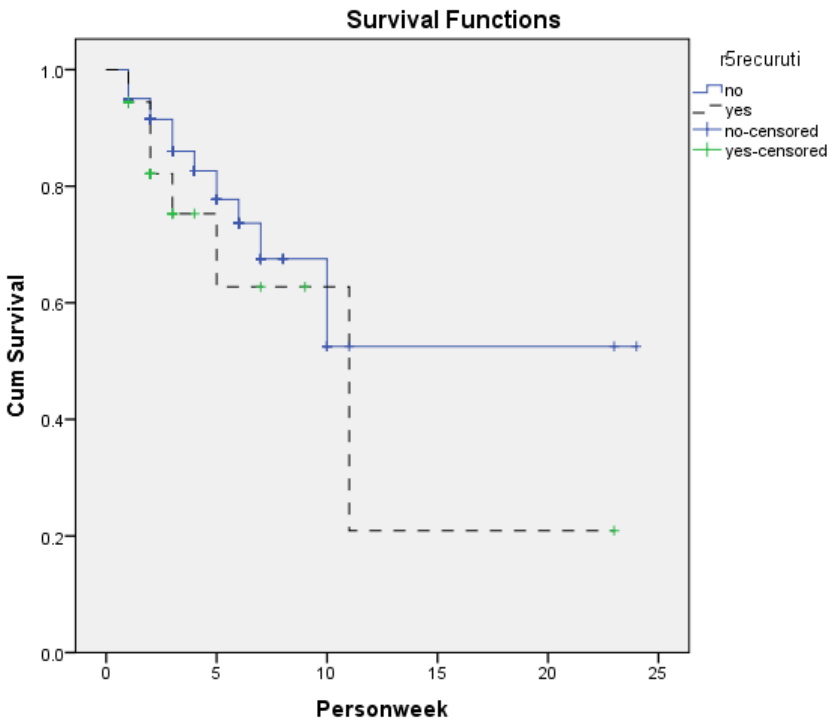


Figure 4.11 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by recurrent urinary tract infection. (p =0.252)

Co-morbidity

Patients with co-morbidity had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients with no co-morbidity significantly, which were 6.0 and 3.8 per 100 person-weeks, respectively (Figure 4.12).

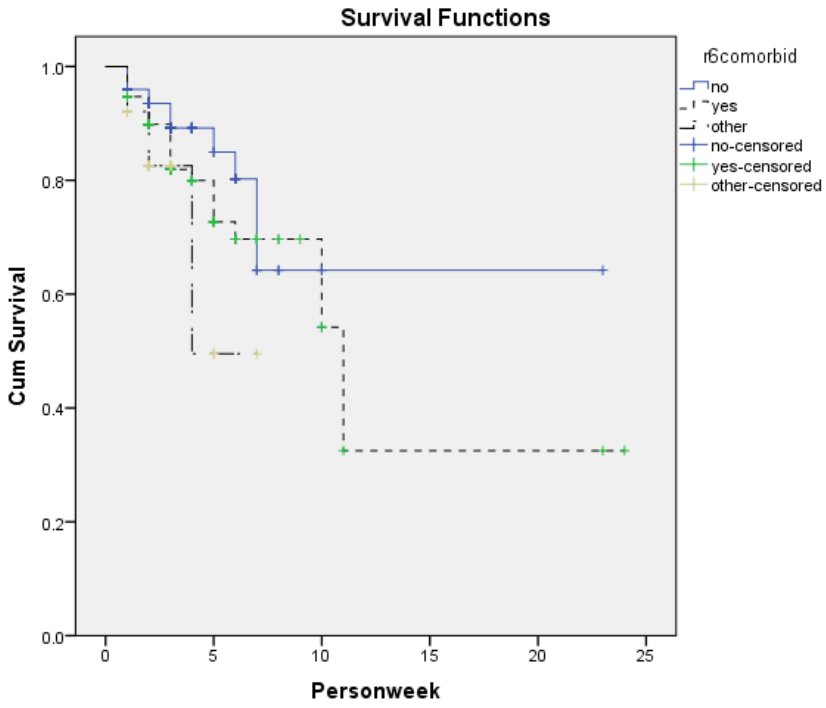


Figure 4.12 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by co-morbidity during this admission. (p =0.042)

Invasive urine catheter during this admission

Patients with invasive urine catheter used during this admission had the higher incidence density of having urinary tract infection with ESBL-producing *E.coli* than among patients with non invasive urine catheter used during this admission significantly, which were 7.8 and 3.6 per 100 persons-week, respectively (Figure 4.13).

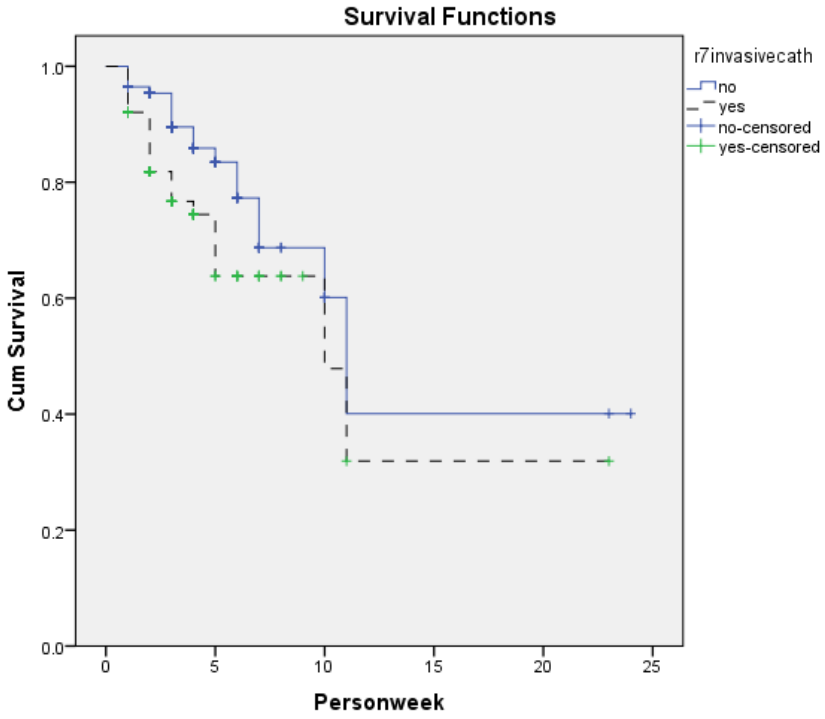


Figure 4.13 Comparison of survival curves of nosocomial urinary tract infection with ESBL-producing *E.coli* by invasive urine catheter during this admission. (p <0.001)

4.6 Crude analysis of associations between factors and ESBL-producing *E.coli* nosocomial urinary tract infection (Table 4.5)

4.6.1 General characteristic

Gender

Females had higher risk to develop incidence of infection by ESBL-producing *E.coli* than males for 2.33 times (HR= 2.33, 95%CI; 1.43-3.80, p=0.001).

Age

The risk of nosocomial urinary tract infection by ESBL-producing *E.coli* in the age group ≥56 years had higher risk than the age group ≤ 55 for 2.49 times (HR=2.49, 95%CI; 1.45-4.32, p=0.001).

Department

Medical ward (HR=0.78, 95%CI; 0.45-1.49, p=0.776), surgical ward (HR=0.32, 95%CI, 0.10-0.99, p=0.315), and intensive care unit (HR=1.30, 95%CI; 0.59-2.85, p=1.291) did not demonstrate significant risk to develop nosocomial urinary tract infection by ESBL-producing *E.coli* more than other wards.

Principle diagnosis

Patients with diagnosis of having chronic non communicable diseases had higher risk to develop nosocomial urinary tract infection by ESBL-producing *E.coli* 5.82 times (HR=5.82, 95%CI; 3.75-9.02, p<0.001) more than those without chronic non communicable diseases.

4.6.2 Clinical risk factors

Prior antibiotic used within last year

Patients who used antibiotic within one year before had higher risk for 7.00 times (HR=7.00, 95%CI; 3.79-12.95, p<0.001) to develop nosocomial urinary tract infection by ESBL-producing *E.coli* more than who did not use antibiotic.

Previous hospitalization

Previous hospitalization did not demonstrate significant risk to develop to develop nosocomial urinary tract infection by ESBL-producing *E.coli* (HR=0.73, 95%CI; 0.43-1.22, p<0.232) more than patients who did not have previous hospitalization.

ICU stay during present admission

Patients who stay in ICU during present admission had lower risk to develop nosocomial urinary tract infection by ESBL-producing *E.coli* for 7.18 times (HR=7.18, 95%CI; 0.99-51.81, p=0.051) more than who never stay in ICU during present admission. However, there was one factor showed a slight p-value (0.051) higher than 0.05. Considering this factor is a discriminant vulnerable for the incidence of ESBL-producing *E.coli* infection. Therefore it is possibly considered as a borderline factor.

Urine catheter used within 30 days

Patients who used urine catheter within 30 days had higher risk for 4.24 times (HR=4.24, 95%CI; 2.71-6.64, p<0.001) to develop nosocomial urinary tract infection by ESBL-producing *E.coli* more than who did not use urine catheter.

Recurrent urinary tract infection

Having recurrent urinary tract infection did not demonstrate significant risk to develop nosocomial urinary tract infection by ESBL-producing *E.coli* (HR= 1.48, 95%CI; 0.74-2.92, p=0.269).

Invasive urine catheter during present admission

Patients with invasive urine catheter during present admission had higher risk for 2.14 times (HR=2.14, 95%CI; 1.40-3.30, p<0.001) to develop nosocomial urinary tract infection by ESBL-producing *E.coli* more than those who did not have invasive urine catheter.

Antibiotic used in the admission

Patients who used antibiotics in the admission had higher risk for 22.18 times (HR=22.18, 95%CI; 7.0-70.3, p<0.001) to develop nosocomial urinary tract infection by ESBL-producing *E.coli* more than who did not use antibiotics.

Co-morbidity

Having co-morbidity did not demonstrate significant risk to develop nosocomial urinary tract infection by ESBL-producing *E.coli* (HR=1.57, 95%CI; 0.99-2.49, p=0.056).

Table 4.5 Crude analysis of the risk factors and ESBL-producing *E.coli* nosocomial urinary tract infection

Factors	Crude HR	95%CI of Crude HR	p-value
General characteristic			
Gender			
Male	1		
Female	2.33	1.43-3.80	0.001*
Age (year)			
≤ 55	1		
≥ 56	2.49	1.45-4.32	0.001*
Department			
Medical ward	0.41	0.15-1.12	0.082
Surgical ward	1.66	0.92-3.01	0.093
Intensive care unit	1.29	0.67-2.47	0.446
Ob-gyn ward	1		
Principle diagnosis			
Chronic disease	5.82	3.75-9.02	<0.001*
Non chronic disease	1		
Clinical risk factors			
Prior antibiotics used within last year			
Yes	7.00	3.75-12.95	<0.001*
No	1		
Urine catheter used within 30 days			
Yes	4.24	2.71-6.64	<0.001*
No	1		
Recurrent urinary tract infection			
Yes	1.48	0.74-2.92	0.269
No	1		
Previous hospitalization			
Yes	0.73	0.43-1.22	0.232
No	1		

Table 4.5 Crude analysis of the risk factors and ESBL-producing *E.coli* nosocomial urinary tract infection (cont.)

Factors	Crude HR	95%CI	p-value
ICU stay during present admission			
ICU stay	1		
Non ICU stay	7.18	0.99-51.81	0.051*
Co-morbidity			
Yes	1.57	0.99-2.49	0.056
No	1		
Invasive urine catheter			
Yes	2.14	1.40-3.30	0.001*
No	1		
Antibiotic used in this admission			
Yes	22.18	7.0-70.3	<0.001*
No	1		

*Statistical significance at $\alpha \leq 0.05$

4.7 Multivariated analysis of association the risk factors and ESBL-producing *E.coli* nosocomial urinary tract infection (Table 4.6)

Cox's proportional hazard regression analysis was used to demonstrate adjusted risk to develop nosocomial urinary tract infection by ESBL-producing *E.coli* among significant factors from univariate analysis which were gender, age group, principle diagnosis, prior antibiotics used within last year, ICU stay during present admission, urine catheter used within 30 days and invasive urine catheter.

The factors were significantly associated with survival time ($p<0.05$) base on multivariate analysis of gender, principle diagnosis, prior antibiotic used within a year before, ICU stay during present admission, urine catheter used within 30 days and invasive urine catheter.

Gender

The risk of nosocomial urinary tract infection by ESBL-producing *E.coli* in female was significantly different when compared to male (HR=1.67, 95%CI; 1.01-2.76, p=0.044).

Principle diagnosis

The risk of nosocomial urinary tract infection by ESBL-producing *E.coli* in patient who had chronic disease was significantly higher risk when compared to who did not had chronic disease (HR=3.02, 95%CI; 1.91-4.78, p<0.001).

Prior antibiotics used within last year

The risk of nosocomial urinary tract infection by ESBL-producing *E.coli* in patient who used antibiotic within last year was significantly higher risk when compared to patient who never used antibiotic within a year before (HR=3.02, 95%CI; 1.58-5.77, p=0.001).

ICU stay during present admission

The risk of nosocomial urinary tract infection by ESBL-producing *E.coli* in patient who never admitted in ICU during present admission was significantly higher risk when compared to patient who admitted in ICU during present admission (HR=8.85, 95%CI; 1.21-64.47, p=0.031).

Urine catheter used within 30 days

The risk of nosocomial urinary tract infection by ESBL-producing *E.coli* in patient who had used urine catheter within 30 days was significantly higher risk when compared to patient who never used urine catheter within 30 days (HR=1.63, 95%CI; 1.01-2.62, p=0.044).

Invasive urine catheter during present admission

The risk of nosocomial urinary tract infection by ESBL-producing *E.coli* in patient who had invasive urine catheter during present admission was significantly different when compared to patient who never had invasive urine catheter during present admission (HR=1.76, 95%CI; 1.13-2.70, p=0.012).

Antibiotic used during present admission

The risk of nosocomial urinary tract infection by ESBL-producing *E.coli* in patient who had used antibiotic during present admission was significantly different when compared to patient who never used antibiotic during present admission (HR=9.82, 95%CI; 3.02-31.97, p<0.001).

Table 4.6 Multiple analysis of the risk factors and ESBL-producing *E.coli* nosocomial urinary tract infection

Factors	Crude HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value
Gender				
Male	1		1	
Female	2.33 (1.43-3.80)	0.001*	1.67 (1.01-2.76)	0.044**
Age group (years)				
≤ 55	1		1	
≥ 56	2.49 (1.45-4.32)	0.001*	1.29 (0.74-2.27)	0.393
Principle diagnosis				
Chronic disease	5.82 (3.75-9.02)	<0.001*	3.02 (1.91-4.78)	<0.001**
Non chronic disease	1		1	
Prior antibiotics used within last year				
Yes	7.00 (3.75-12.95)	<0.001*	3.02 (1.58-5.77)	0.001**
No	1		1	
ICU stay during present admission				
ICU stay	1		1	
Non ICU stay	7.18 (0.99 –51.81)	0.051	8.85 (1.21-64.47)	0.031**
Urine catheter used within 30 days				
Yes	4.24 (2.71 – 6.64)	<0.001*	1.63 (1.01-2.62)	0.044**
No	1		1	

***** Statistical significance at α ≤0.05

** Adjust HR= adjusted all variable in the table

Table 4.6 Multiple analysis of the risk factors and ESBL-producing *E.coli* nosocomial urinary tract infection (cont.)

Factors	Crude HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value**
Invasive urine catheter				
Yes	2.14(1.40-3.30)	0.001*	1.76(1.13-2.70)	0.012**
No	1		1	
Antibiotic used during present admission				
Yes	22.18(7.00-70.30)	<0.001*	9.82 (3.02-31.97)	<0.001**
No	1		1	

***** Statistical significance at $\alpha \leq 0.05$

** Adjust HR= adjusted all variable in the table

4.8 Antimicrobial susceptibility of ESBL producing-*E.coli* infection

ESBL producing-*E.coli* was 100% resisted to Ampicillin, 98.8% resisted to Cefuroxime and Ciprofloxacin, 97.5% resisted to and Cefpirome and mostly were sensitive to Meropenem and Ertapenem 100%. The sensitivity to Cefroxime, Cepfotaxime and Ceftazidime were very low as 1.3%. (Table 4.7)

Table 4.7 Antimicrobial susceptibility of ESBL-producing *E.coli* infection

	Susceptible		Resistance		Intermediate	
	n	%	n	%	n	%
Amikacin	71	92.3	2	2.6	4	5.2
Gentamicin	24	31.2	52	67.6	1	1.3
Netilmycin	56	72.8	9	11.7	12	15.6
Ampicillin	-	-	77	100	-	-
Amoxacillin/clavu	20	26.0	31	40.3	26	33.8
Cefoperazone/Sulb	40	52	12	15.6	25	32.5

Table 4.7 Antimicrobial susceptibility of ESBL-producing *E.coli* infection (cont.)

	Susceptible		**Resistance**		**Intermediate**	
	n	**%**	**n**	**%**	**n**	**%**
Cephalothin	3	3.9	70	91	4	5.2
Cefuroxime	1	1.3	76	98.8	-	-
Cepfoxitin	61	79.3	14	18.2	2	2.6
Cepfotaxime	1	1.3	58	75.4	-	-
Ceftazidime	1	1.3	58	75.4	-	-
Cefpirome	2	2.6	75	97.5	-	-
Imipenem	75	97.5	2	2.6	-	-
Meropenem	77	100	-	-	-	-
Ertapenem	77	100	-	-	-	-
Ciprofloxacin	-	-	76	98.8	1	1.3
Trimetro/sulfa	12	18.18	63	81.82	-	-
Tetracyclin	13	16.9	64	83.2	-	-
Piperaci/Tazob	57	74.1	14	18.2	6	7.8
Doripenem	70	90.91	7	9.1	-	-

CHAPTER V
DISCUSSIONS

This retrospective cohort study was carried out among inpatients with urinary tract infection after 48 hours of admission at Taksin Hospital, Bangkok Metropolitan Administration during January to December 2011. The objectives of the study were to assess the incidence density and its risk factors of ESBL-producing *E.coli* nosocomial infection. Data collection was performed through medical records reviewing.

5.1 Statements of the principle findings

Result from this study demonstrated overall incidence density of ESBL-producing *E.coli* infection among this group of patients was 5.1 per 100 person weeks when incidence density among males (3.0 per 100 person week) was lower than among female patients (6.7 per 100 person week). However, results from previous study in China found that male patients had higher incidence of ESBL-producing *E.coli* than female patients (66.7% vs. 23.9%; p=0.005) (61). Other study in Thailand also found incidence among females with the ESBL-producing *E.coli* was higher than males (15). However, females usually had more complicate of urinary tract system than males, and female more prone to infection by extended spectrum beta lactamase-producing *E.coli* than male.

Previous study found that the used of antibiotic in last 1 month was a risk factor for ESBL infection (OR=3.08, 95%CI; 1.63-5.83, p=0.001) (63), and within the year was also a risk factors for ESBL-producing strain infection (OR 3.03, 95%CI; 1.33-7.68, p=0.006) (64). Study in Thailand found that the previous using of antibiotics, especially third-generation Cephalosporins and Fluoroquinolones was the risk factors for community-onset ESBL-producing *E.coli* infection (15). Besides, it also reported the recent receipt of antibiotics (<90 days) (OR 15.1, 95%CI; 4.2-44.2,

p=0.004) (68). There was also study in Thailand reported prior exposure to Cephalosporins (OR 3.92, 95%CI; 2.72-6.77) (68). It was also found that the previous using Cephalosporins groups was significant risk factor (OR=4.52 95%CI; 1.44 – 14.25, p=0.01) (68). Our study supported the above studies that the use of Cephalosporins group were the risk factor for ESBL infection. It was explained that prolong used of several types of antibiotics was potential for plasmid-mediated resistance to those antibiotics by the mutation of agents.

Urine catheter used within 30 days was also one of the risk factor for ESBL-producing *E.coli* (OR=6.28, 95%CI; 1.86 - 21.02, p<0.001) (59). Previous study found that the used of urinary catheter was major risk factor for ESBL infection (OR=4.28, 95%CI; 2.21-8.29, p<0.001) (63). It also reported from previous study that patients with indwelling urinary catheters had higher proportion of ESBL nosocomial infection compared to who did not (41.7% vs 6.5%; p=0.002) (61). In previous study, it also found that risk of nosocomial urinary tract infection by ESBL-producing *E.coli* of patient who had used urine catheter within 30 days was 4.24 times (OR=4.24, 95%CI; 2.71-6.64, p<0.001) (61). Our study supported that the use of catheter within 30 days was the risk factor for ESBL-producing *E.coli.* It was known that one route of urinary tract infection was indwelling urinary catheter when using the antibiotic for treatment supported this infection.

ICU stay was an acquisition risk factors for that infection from previous study (OR=2.55, 95%CI; 1.10-5.90) (64). But this study did not found that urine catheter used, having diabetes mellitus, having malignoma and having co-morbidities associated with increasing risk (64). Study in India, it was also found that an admission in intensive care unit was not associated with urinary tract infection (OR=2.16, 95%CI; 0.98-4.73) (63). But study in China found higher proportion of patients who had prior ICU admission in patients with ESBL-producing *E.coli* than in non ESBL-producing *E.coli* group (41.7% vs. 4.4%, p=0.003) (61). In our study, we found that patients who did not stay in ICU but in other wards such as surgery and medicine had higher risk for nosocomial urinary tract infection by ESBL-producing *E.coli* than patient who had stayed in ICU (HR=0.14, 95%CI; 0.02-1.01, p=0.051). These was due to ICU had better or stronger practice in infection control standard and had higher ratio of nurse per patient than other wards in Taksin hospital.

The retrospective study found that having some chronic diseases and recurrent of UTI were also the risk factors for nosocomial urinary tract infection from ESBL-producing *E.coli* (p=0.032) (52). Previous studies found that urinary tract disorder was a acquisition risk factor for ESBL-producing *E.coli* infection (OR=2.30, 95%CI; 1.21-4.35, p=0.009) (52), but chronic renal failure did not enhance the risk for ESBL-producing *E.coli* infection (52). In our study, it was also found that the risk of nosocomial urinary tract infection by ESBL-producing *E.coli* of patient who had chronic disease was 3.02 times (HR=3.02, 95%CI; 1.91-4.78, p<0.001) compared to who did not have chronic diseases. Multiple admission, prolong stayed in hospital and often used of antibiotic among patients with chronic diseases were the main reasons for low immunity and became susceptible to nosocomial infection by ESBL-producing *E.coli* infection.

Using urinary catheter when became invasive, it is also risk factor of ESBL-producing *E.coli* infection. In our study, it was found invasive indwelling urine catheter was the risk of nosocomial urinary tract infection by ESBL-producing *E.coli* (OR=17.76 95%CI; 1.13-2.73, p=0.012). This finding was not consistent with previous retrospective study (52). The contamination during procedure of indwelling was not good enough for infection control, long term use of this device.

In these set of data, factors did not demonstrate risk factors for ESBL-producing *E.coli* nosocomial infection in urinary tract in crude analysis were recurrent of urinary tract infection, previous hospitalization, and patient's co-morbidity. Age group did not demonstrate risk factors for ESBL-producing *E.coli* infection in multivariate analysis.

5.2 Strength and weakness of the study

5.2.1 Strength of the study

1) The study design was the retrospective cohort study which is considered as good disease occurrence consequence of factors to outcome monitoring with person-time concept. It is more useful information than using prevalent cases.

2) Site of the study was only in one hospital of BMA with high standard of medical record system for training BMA medical students. So valid and precise data can be achieved to fulfill the usefulness of the results of this study.

5.2.2 Weakness of the study

1) Study plan did not perform at the beginning of study earlier, some of variables related to risk factors of this ESBL-producing *E.coli* nosocomial infection in urinary tract were not included such as severity of illness.

2) Some clinical data in this study were mainly based on hospital records in the past, confirmation by direct interview can not be done.

CHAPTER VI
CONCLUSION AND RECOMMENDATION

Conclusion

This retrospective cohort study among inpatients who had admitted during 1 January 2011 to 31 December 2011 at Taksin hospital, Bangkok Metropolitan Administration. The purposes of this study were to assess incidence density and to identify factors associated with nosocomial urinary tract infection by extended-spectrum beta lactamase-producing *E.coli*. Data were collected from existing medical records.

Study population were 937 patients who admitted in hospital more than 48 hours with urine culture positive, there were 197 cases positive by *E.coli*, 349 positive for other organism. Among 197 patients who were positive by *E.coli*, 83 patients were ESBL-producing *E.coli*. With person-weeks in 1644, the overall incidence density was 5.1 per 100 person per week.

Factors associated with nosocomial urinary tract infection by extended-spectrum beta lactamase-producing *E.coli* were gender (HR=1.67; 95%CI; 1.01-2.76), principle diagnosis (HR=3.02; 95%CI; 1.91-4.78), prior antibiotic used within last year (HR=3.02; 95%CI; 1.58-5.77), ICU stay during present admission (HR=8.85; 95%CI; 1.21-64.47), urine catheter used within 30 days (HR=1.63; 95%CI; 1.01-2.62) and invasive urine catheter during present admission (HR=1.76; 95%CI; 1.13-2.73), antibiotic used during present admission (HR=9.82; 95%CI; 3.02-31.97).

Recommendation for the implication of the results

To prevent and to control nosocomial urinary tract infection by extended spectrum beta-lactamase-producing *E.coli* it is recommended for;

1. Carefully treat for high risk group who are:

1.1 Patients with the chronic diseases especially diabetes mellitus and chronic renal disease as the risk factors.

1.2 Patients using invasive urine catheter, invasive use should be considered whenever necessary and utilize it for limited period.

2. Reasonable use of prescribed antibiotics for treatment of infection.

3. Improvement in practice of clinical care in accordance with the infection control standard especially in surgical, medicine and ob-gyn admitted wards.

4. Antibiotic drugs administration is strongly recommended for its proper and effective utilization regimen based on antibiogram and sensitivity report to avoid a development of undesirable drug resistance.

Recommendation for further study:

1. The further study should include the exclusion criteria patients who had others infection during urine culture collection for reliability and specificity of primary source of infection data.

2. The further study should be aimed to evaluate prescription pattern and cost of broad-spectrum antibiotics listed in the Drug Use Evaluation (DUE) program in Taksin hospital, Bangkok Metropolitan Administration.

REFERENCES

1. Reinthaler FF, Feierl G, Galler H, Haas D, Leitner E, Mascher F, et al. ESBL-producing *E. coli* in Austrian sewage sludge. Water Research 2010; 44: 1981-5.
2. Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing *E-coli* compared to non-ESBL producing *E-coli.* Journal of Infection 2007; 55: 254-9.
3. Falagas ME, Karageorgopoulos DE. Extended-spectrum beta-lactamase-producing organisms. Journal of Hospital Infection 2009; 73: 345-54.
4. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev 2005; 18: 657-86.
5. Pena C, Gudiol C, Calatayud L, Tubau F, Dominguez MA, Pujol M, et al. Infections due to *Escherichia coli* producing extended-spectrum beta-lactamase among hospitalised patients: factors influencing mortality. Journal of Hospital Infection 2008; 68: 116-22.
6. Dhillon RH, Clark J. ESBLs: A Clear and Present Danger? Crit Care Res Pract 2012; 2012: 625170.
7. Kliebe C, Nies BA, Meyer JF, Tolxdorff-Neutzling RM, Wiedemann B. Evolution of plasmid-coded resistance to broad-spectrum cephalosporins. Antimicrob Agents Chemother 1985; 28: 302-7.
8. Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of *Klebsiella pneumoniae* and *Serratia marcescens.* Infection 1983; 11: 315-7.
9. Pitout JD, Nordmann P, Laupland KB, Poirel L. Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. J Antimicrob Chemother 2005; 56: 52-9.
10. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004; 32: 470-85.

11. Turner PJ, Greenhalgh JM, Edwards JR, McKellar J. The MYSTIC (meropenem yearly susceptibility test information collection) programme. Int J Antimicrob Agents 1999; 13: 117-25.

12. Bell JM, Turnidge JD, Gales AC, Pfaller MA, Jones RN. Prevalence of extended spectrum beta-lactamase (ESBL)-producing clinical isolates in the Asia-Pacific region and South Africa: regional results from SENTRY Antimicrobial Surveillance Program (1998-99). Diagn Microbiol Infect Dis 2002; 42: 193-8.

13. A.Dechphipat MP, J. Puangmanee, S.Ampi and N.Wipatsara. The prevalence of extebdd-spectrum beta-lactamases producing in *Klebsiella pneumonia* and *Escherichia coli* isolated from patients attendind in Nan Hospital and Community Hospital in Nan province, Thailand (2004-2010). วารสารเทคนิคการแพทย์เชียงใหม่ 2011; 3: 169.

14. Philippon A, Labia R, Jacoby G. Extended-spectrum beta-lactamases. Antimicrob Agents Chemother 1989; 33: 1131-6.

15. Apisarnthanarak A, Kiratisin P, Saifon P, Kitphati R, Dejsirilert S, Mundy LM. Clinical and molecular epidemiology of community-onset, extended spectrum beta-lactamase-producing *Escherichia coli* infections in Thailand: A case-case-control study. Am J Infect Control 2007; 35: 606-12.

16. Polwichai P, Trakulsomboon S, Dejsirilert S, Thongmali O, Sawanpanyalert P, Aswapokee N, et al. Long-term study of *Escherichia coli* and *Klebsiella pneumoniae* isolates producing extended-spectrum beta-lactamases. J Med Assoc Thai 2009; 92 Suppl 4: S53-8.

17. organization wh. Prevention of hospital-acquired infections: a practical guide. 2002.

18. Pitout JDD, Laupland KB. Extended-spectrum beta-lactamase-producing enterobacteriaceae: an emerging public-health concern. Lancet Infectious Diseases 2008; 8: 159-66.

19. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988; 16: 128-40.

20. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Am J Infect Control 1992; 20: 271-4.

21. Coffin SE, Zaoutis TE. Infection control, hospital epidemiology, and patient safety. Infect Dis Clin North Am 2005; 19: 647-65.
22. Wilke MS, Lovering AL, Strynadka NC. Beta-lactam antibiotic resistance: a current structural perspective. Curr Opin Microbiol 2005; 8: 525-33.
23. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother 2010; 54: 969-76.
24. Jacoby GA. AmpC beta-lactamases. Clin Microbiol Rev 2009; 22: 161-82, Table of Contents.
25. Bush K, Jacoby GA, Medeiros AA. A functional classification scheme for beta-lactamases and its correlation with molecular structure. Antimicrob Agents Chemother 1995; 39: 1211-33.
26. Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 2001; 14: 933-51, table of contents.
27. Christophers J, Sutton RN. Characterisation of acyclovir-resistant and -sensitive clinical herpes simplex virus isolates from an immunocompromised patient. J Antimicrob Chemother 1987; 20: 389-98.
28. Gutmann L, Ferre B, Goldstein FW, Rizk N, Pinto-Schuster E, Acar JF, et al. SHV-5, a novel SHV-type beta-lactamase that hydrolyzes broad-spectrum cephalosporins and monobactams. Antimicrob Agents Chemother 1989; 33: 951-6.
29. Ben Redjeb S, Ben Yaghlane H, Boujnah A, Philippon A, Labia R. Synergy between clavulanic acid and newer beta-lactams on nine clinical isolates of Klebsiella pneumoniae, *Escherichia coli* and *Salmonella typhimurium* resistant to third-generation cephalosporins. J Antimicrob Chemother 1988; 21: 263-6.
30. Cooksey R, Swenson J, Clark N, Gay E, Thornsberry C. Patterns and mechanisms of beta-lactam resistance among isolates of *Escherichia coli* from hospitals in the United States. Antimicrob Agents Chemother 1990; 34: 739-45.
31. Rice LB, Willey SH, Papanicolaou GA, Medeiros AA, Eliopoulos GM, Moellering RC, Jr., et al. Outbreak of ceftazidime resistance caused by extended-spectrum beta-lactamases at a Massachusetts chronic-care facility. Antimicrob Agents Chemother 1990; 34: 2193-9.

32. Palucha A, Mikiewicz B, Hryniewicz W, Gniadkowski M. Concurrent outbreaks of extended-spectrum beta-lactamase-producing organisms of the family Enterobacteriaceae in a Warsaw hospital. J Antimicrob Chemother 1999; 44: 489-99.
33. Szabo D, Filetoth Z, Szentandrassy J, Nemedi M, Toth E, Jeney C, et al. Molecular epidemiology of a cluster of cases due to *Klebsiella pneumoniae* producing SHV-5 extended-spectrum beta-lactamase in the premature intensive care unit of a Hungarian hospital. J Clin Microbiol 1999; 37: 4167-9.
34. Venezia RA, Scarano FJ, Preston KE, Steele LM, Root TP, Limberger R, et al. Molecular epidemiology of an SHV-5 extended-spectrum beta-lactamase in enterobacteriaceae isolated from infants in a neonatal intensive care unit. Clinical Infectious Diseases 1995; 21: 915-23.
35. Bermudes H, Arpin C, Jude F, el-Harrif Z, Bebear C, Quentin C. Molecular epidemiology of an outbreak due to extended-spectrum beta-lactamase-producing enterobacteria in a French hospital. Eur J Clin Microbiol Infect Dis 1997; 16: 523-9.
36. Gniadkowski M, Palucha A, Grzesiowski P, Hryniewicz W. Outbreak of ceftazidime-resistant Klebsiella pneumoniae in a pediatric hospital in Warsaw, Poland: clonal spread of the TEM-47 extended-spectrum beta-lactamase (ESBL)-producing strain and transfer of a plasmid carrying the SHV-5-like ESBL-encoding gene. Antimicrob Agents Chemother 1998; 42: 3079-85.
37. Shannon K, Fung K, Stapleton P, Anthony R, Power E, French G. A hospital outbreak of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* investigated by RAPD typing and analysis of the genetics and mechanisms of resistance. Journal of Hospital Infection 1998; 39: 291-300.
38. Gaillot O, Maruejouls C, Abachin E, Lecuru F, Arlet G, Simonet M, et al. Nosocomial outbreak of Klebsiella pneumoniae producing SHV-5 extended-spectrum beta-lactamase, originating from a contaminated ultrasonography coupling gel. J Clin Microbiol 1998; 36: 1357-60.

39. Tzelepi E, Magana C, Platsouka E, Sofianou D, Paniara O, Legakis NJ, et al. Extended-spectrum beta-lactamase types in *Klebsiella pneumoniae* and *Escherichia coli* in two Greek hospitals. Int J Antimicrob Agents 2003; 21: 285-8.
40. Hirakata Y, Matsuda J, Miyazaki Y, Kamihira S, Kawakami S, Miyazawa Y, et al. Regional variation in the prevalence of extended-spectrum beta-lactamase-producing clinical isolates in the Asia-Pacific region (SENTRY 1998-2002). Diagn Microbiol Infect Dis 2005; 52: 323-9.
41. Rodriguez-Bano J, Navarro MD, Romero L, Martinez-Martinez L, Muniain MA, Perea EJ, et al. Epidemiology and clinical features of infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in nonhospitalized patients. J Clin Microbiol 2004; 42: 1089-94.
42. Mugnaioli C, Luzzaro F, De Luca F, Brigante G, Perilli M, Amicosante G, et al. CTX-M-type extended-spectrum beta-lactamases in Italy: molecular epidemiology of an emerging countrywide problem. Antimicrob Agents Chemother 2006; 50: 2700-6.
43. Pournaras S, Ikonomidis A, Sofianou D, Tsakris A, Maniatis AN. CTX-M-type beta-lactamases affect community *Escherichia coli* treatment, Greece. Emerg Infect Dis 2004; 10: 1163-4.
44. Woodford N, Ward ME, Kaufmann ME, Turton J, Fagan EJ, James D, et al. Community and hospital spread of *Escherichia coli* producing CTX-M extended-spectrum beta-lactamases in the UK. J Antimicrob Chemother 2004; 54: 735-43.
45. Pitout JD, Church DL, Gregson DB, Chow BL, McCracken M, Mulvey MR, et al. Molecular epidemiology of CTX-M-producing *Escherichia coli* in the Calgary Health Region: emergence of CTX-M-15-producing isolates. Antimicrob Agents Chemother 2007; 51: 1281-6.
46. Ben-Ami R, Schwaber MJ, Navon-Venezia S, Schwartz D, Giladi M, Chmelnitsky I, et al. Influx of extended-spectrum beta-lactamase-producing enterobacteriaceae into the hospital. Clinical Infectious Diseases 2006; 42: 925-34.

47. Rodriguez-Bano J, Navarro MD, Romero L, Muniain MA, de Cueto M, Rios MJ, et al. Bacteremia due to extended-spectrum beta -lactamase-producing *Escherichia coli* in the CTX-M era: a new clinical challenge. Clinical Infectious Diseases 2006; 43: 1407-14.

48. อนุชา อภิสารธนรักษ์. ตำราระบาดวิทยาและมาตรการควบคุมของเชื้อจุลชีพดื้อยาในโรงพยาบาล. พิมพ์ครั้งที่ 1: กรุงเทพเวชสาร; 2554. 142 p.

49. Pitout JDD. Infections with Extended-Spectrum beta-Lactamase-Producing Enterobacteriaceae Changing Epidemiology and Drug Treatment Choices. Drugs 2010; 70: 313-33.

50. Hawser SP, Bouchillon SK, Hoban DJ, Badal RE, Hsueh PR, Paterson DL. Emergence of high levels of extended-spectrum-beta-lactamase-producing gram-negative bacilli in the Asia-Pacific region: data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program, 2007. Antimicrob Agents Chemother 2009; 53: 3280-4.

51. Lopez-Cerro L PA. Epidemiology of ESBL in the community. An increasing problem. Enferm infect Mcrobiol Clin 2007; 25(s2).

52. Briongos-Figuero LS, Gomez-Traveso T, Bachiller-Luque P, Dominguez-Gil Gonzalez M, Gomez-Nieto A, Palacios-Martin T, et al. Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. Int J Clin Pract 2012; 66: 891-6.

53. Wagenlehner FM, Niemetz AH, Weidner W, Naber KG. Spectrum and antibiotic resistance of uropathogens from hospitalised patients with urinary tract infections: 1994-2005. Int J Antimicrob Agents 2008; 31 Suppl 1: S25-34.

54. Wagenlehner FME, Cek M, Naber KG, Kiyota H, Bjerklund-Johansen TE. Epidemiology, treatment and prevention of healthcare-associated urinary tract infections. World Journal of Urology 2012; 30: 59-67.

55. Meier S, Weber R, Zbinden R, Ruef C, Hasse B. Extended-spectrum beta-lactamase-producing Gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy. Infection 2011; 39: 333-40.

56. Perez F, Endimiani A, Hujer KM, Bonomo RA. The continuing challenge of ESBLs. Curr Opin Pharmacol 2007; 7: 459-69.
57. Saely S, Kaye KS, Fairfax MR, Chopra T, Pogue JM. Investigating the impact of the definition of previous antibiotic exposure related to isolation of extended spectrum beta-lactamase-producing *Klebsiella pneumoniae*. Am J Infect Control 2011; 39: 390-5.
58. Wiegand I, Geiss HK, Mack D, Sturenburg E, Seifert H. Detection of extended-spectrum beta-lactamases among Enterobacteriaceae by use of semiautomated microbiology systems and manual detection procedures. J Clin Microbiol 2007; 45: 1167-74.
59. Extended-spectrum beta-lactamases ingram negative bacteria. J Glob Infect Dis 2010; 2(3): 263-74.
60. Wayne P. National Committee for Clinical Laboratory Standards.2005. Performance standards for antimicrobial susceptibility testing:15th informational supplement(M100-S15). National Committee for Clinical Laboratory Standard 2005.
61. Yang YS, Ku CH, Lin JC, Shang ST, Chiu CH, Yeh KM, et al. Impact of Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae on the outcome of community-onset bacteremic urinary tract infections. J Microbiol Immunol Infect 2010; 43: 194-9.
62. Mansouri M, Ramazanzadeh R, Norabadi P. Cefepime resistance and associated risk factors among Escherichia coli strains isolated from clinical specimens. Chemotherapy 2011; 57: 134-7.
63. Goyal A, Prasad KN, Prasad A, Gupta S, Ghoshal U, Ayyagari A. Extended spectrum beta-lactamases in *Escherichia coli* & *Klebsiella pneumoniae* & associated risk factors. Indian J Med Res 2009; 129: 695-700.
64. Kuster SP, Hasse B, Huebner V, Bansal V, Zbinden R, Ruef C, et al. Risks Factors for Infections with Extended-Spectrum Beta-Lactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae* at a Tertiary Care University Hospital in Switzerland. Infection 2010; 38: 33-40.
65. Rawat D, Nair D. Extended-spectrum beta-lactamases in Gram Negative Bacteria. J Glob Infect Dis 2010; 2: 263-74.

66. Van der Starre WE, van Nieuwkoop C, Paltansing S, van't Wout JW, Groeneveld GH, Becker MJ, et al. Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection. J Antimicrob Chemother 2011; 66: 650-6.

67. Aguilar-Duran S, Horcajada JP, Sorli L, Montero M, Salvado M, Grau S, et al. Community-onset healthcare-related urinary tract infections: comparison with community and hospital-acquired urinary tract infections. J Infect 2012; 64: 478-83.

68. Chaiwarith R, Pasogpakdee P, Salee P, Kanjanaratanakorn K, Sirisanthana T, Supparatpinyo K. Risk factors for extended-spectrum beta-lactamase-producing Klebsiella pneumoniae and Escherichia coli acquisition in a tertiary care teaching hospital in Thailand. The Journal of hospital infection 2009; 71(3): 285-6.

69. Van der Starre WE, van Nieuwkoop C, Paltansing S, van't Wout JW, Groeneveld GH, Becker MJ, et al. Risk factors for fluoroquinolone-resistant Escherichia coli in adults with community-onset febrile urinary tract infection. The Journal of antimicrobial chemotherapy 2011; 66(3): 650-6.

70. Pena C, Pujol M, Ricart A, Ardanuy C, Ayats J, Linares J, *et al*. Risk factors for faecal carriage of Klebsiella pneumoniae producing extended spectrum beta-lactamase (ESBL-KP) in the intensive care unit. J Hosp Infect 1997; 35:9-16.

71. Pitout JDD, Laupland KB. Extended-spectrum beta-lactamase-producing enterobacteriaceae: an emerging public-health concern. Lancet Infectious Diseases 2008; 8: 159-66.

APPENDIX

บัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล

ใบรับรอง เพื่อแสดงว่า

ชื่อ – นามสกุล นางสมหญิง ทิพย์มงคล รหัสนักศึกษา ๕๔๓๖๐๙๕ PHPH/M

คณะ / สถาบัน / วิทยาลัย คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

เป็นผู้ผ่านการเรียนชั่วโมง " จริยธรรมการวิจัยในคน "

ในรายวิชา สศชส ๖๓๐ วิธีการวิจัยทางวิทยาศาสตร์สุขภาพ

คณะ / สถาบัน / วิทยาลัย คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

เมื่อวันที่ ๑๐ เดือน กรกฎาคม พ.ศ. ๒๕๕๕

ลงนาม .....

(รองศาสตราจารย์ ดร.ปรารถนา สถิตย์วิภาวี)

อาจารย์ผู้รับผิดชอบรายวิชา

ลงนาม .....

(รองศาสตราจารย์ ดร.สุธรรม นันทมงคลชัย)

อาจารย์ผู้สอน

คำสั่ง
บัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล
ที่ (ทพ) ๔๔๓ / ๒๕๕๖
เรื่อง อนุมัติหัวข้อวิทยานิพนธ์ และแต่งตั้งคณะกรรมการที่ปรึกษาวิทยานิพนธ์

บัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล อนุมัติให้ นางสมหญิง ทิพย์มงคล เลขประจำตัว ๕๔๓๖๐๙๕ PHPH/M นักศึกษาหลักสูตรปริญญาโท สาขาวิชาเอกโรคติดเชื้อและวิทยาการระบาด คณะสาธารณสุขศาสตร์ ศึกษาค้นคว้าเขียนวิทยานิพนธ์ ด้วยภาษาอังกฤษ ในหัวข้อเรื่อง "INCIDENCE AND RISK FACTORS OF EXTENDED-SPECTRUM BETA-LACTAMASE-PRODUCING E.COLI NOSOCOMIAL INFECTION FROM URINE CULTURE IN 2011 AMONG INPATIENTS AT TAKSIN HOSPITAL BANGKOK METROPOLITAN ADMINISTRATION" และขอแต่งตั้งคณะกรรมการที่ปรึกษาวิทยานิพนธ์ ดังนี้

๑. รองศาสตราจารย์ ทพญ.กุลยา นาคสวัสดิ์	อาจารย์ที่ปรึกษาหลัก
๒. รองศาสตราจารย์ดุสิต สุจิรารัตน์	อาจารย์ที่ปรึกษาร่วม
๓. แพทย์หญิงสุพรรณี จิรจริยาเวช	อาจารย์ที่ปรึกษาร่วม (ผู้ทรงคุณวุฒิภายนอก)

คณะกรรมการที่ปรึกษาวิทยานิพนธ์ มีหน้าที่ ดังนี้

๑. รับผิดชอบและควบคุมการทำวิทยานิพนธ์ของนักศึกษา ให้สอดคล้องกับโครงร่างวิทยานิพนธ์ที่นักศึกษาสอบผ่านจากการสอบโครงร่างวิทยานิพนธ์ ที่บัณฑิตวิทยาลัยมีคำสั่งสอบ

๒. ให้คำแนะนำและเป็นที่ปรึกษาแก่นักศึกษาเกี่ยวกับเนื้อหาทางทฤษฎี แนวคิด และวิธีการศึกษาวิจัย รวมทั้งการแก้ไขปัญหาที่เกิดขึ้น

๓. ให้คำแนะนำและเป็นที่ปรึกษาแก่นักศึกษาเกี่ยวกับการเขียนวิทยานิพนธ์และการใช้ภาษา

๔. ติดตามการดำเนินการวิจัยให้เป็นไปตามแผนงานและรับผิดชอบ ประเมินผลการทำวิทยานิพนธ์ทุกภาคการศึกษาจนกว่าการทำวิทยานิพนธ์แล้วเสร็จ

๕. ผู้ที่เป็นอาจารย์ที่ปรึกษาวิทยานิพนธ์หลัก ต้องให้ความเห็นชอบในการขอสอบวิทยานิพนธ์ของนักศึกษาและต้องร่วมเป็นกรรมการสอบวิทยานิพนธ์ของนักศึกษา

๖. ผู้ที่เป็นอาจารย์ที่ปรึกษาวิทยานิพนธ์ร่วม อาจร่วมเป็นกรรมการสอบวิทยานิพนธ์ได้และต้องเข้าสอบวิทยานิพนธ์ของนักศึกษาทุกครั้ง

ทั้งนี้ตั้งแต่บัดนี้ เป็นต้นไป

สั่ง ณ วันที่ ๑๗ พฤษภาคม พ.ศ. ๒๕๕๖

(รองศาสตราจารย์ ทพญ.ดร.อารยา พงษ์หาญยุทธ)
รองคณบดีฝ่ายวิชาการ
ปฏิบัติงานแทน คณบดีบัณฑิตวิทยาลัย

สำเนาเรียน คณะกรรมการที่ปรึกษาวิทยานิพนธ์

บฑ. 33 ผลการสอบโครงร่างวิทยานิพนธ์ / สารนิพนธ์

หลักสูตร ☑ ปริญญาโท ☐ ปริญญาเอก สาขาวิชา โรคติดเชื้อและวิทยาการระบาด

คณะ/สถาบัน/วิทยาลัย สาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

ชื่อนักศึกษา นาย/นาง/นางสาว/ยศ/ สมหญิง พันธุ์มงคล

เลขประจำตัว 5436095 PHPH /M

หลักสูตร ☑ ปกติ ☐ นานาชาติ ☐ ภาคพิเศษ

แผนการศึกษา ☑ เรียนรายวิชาและทำวิทยานิพนธ์ ☐ เรียนรายวิชาและทำสารนิพนธ์ ☐ ทำเฉพาะวิทยานิพนธ์

สอบโครงร่างวิทยานิพนธ์/สารนิพนธ์ หัวข้อเรื่อง

หัวข้อเรื่อง : กรุณาเขียนตัวบรรจง ภาษาอังกฤษเขียนด้วยตัวพิมพ์ใหญ่เท่านั้น

(ภาษาอังกฤษ) INCIDENCE AND RISK FACTORS OF EXTENDED-SPECTRUM BETA LACTAMASE-PRODUCING ESCHERICHIA COLI IN URINE CULTURE AMONG INPATIENTS AT TAKSIN HOSPITAL BANGKOK METROPOLITAN ADMINISTRATION THAILAND

(ภาษาไทย) อัตราอุบัติการณ์และปัจจัยเสี่ยงของการติดเชื้อ E. coli ที่สร้างเอนไซม์ ESBL ในปัสสาวะของผู้ป่วยใน โรงพยาบาลตากสิน สำนักการแพทย์ กรุงเทพมหานคร

สอบโครงร่างวิทยานิพนธ์/สารนิพนธ์ วันที่ 29 เมษายน 2556 เวลา 13.30-16.00 น.

สถานที่สอบ ภาควิชาระบาดวิทยา คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

มติของคณะกรรมการสอบโครงร่างวิทยานิพนธ์ / สารนิพนธ์ ตัดสินผลการสอบของนักศึกษา ดังนี้

☑ ผ่าน

☐ ผ่านโดยมีเงื่อนไข (ระบุเงื่อนไข และระยะเวลาซึ่งต้องไม่เกิน 90 วัน สำหรับวิทยานิพนธ์และไม่เกิน 30 วันสำหรับสารนิพนธ์) ....

☐ ไม่ผ่าน นักศึกษาต้องลงทะเบียนขอสอบใหม่ ภายในไม่เกินวันที่ ....

ลงนามรับรองผลการสอบข้างต้น

1. ลายมือชื่อ [signature] ประธานกรรมการ
   อ. / ผศ. / รศ. / ศ. ทพญ. ภูษา เกตุรัตน์ (เขียนชื่อ-สกุลตัวบรรจง)
   วันที่ ....
2. ลายมือชื่อ [signature] กรรมการ
   อ. / ผศ. / รศ. / ศ. ดุสิต สุจิรารัตน์ (เขียนชื่อ-สกุลตัวบรรจง)
   วันที่ ....
3. ลายมือชื่อ [signature] กรรมการ
   อ. / ผศ. / รศ. / ศ. พญ. สุพรรณี สิริวรรณ (เขียนชื่อ-สกุลตัวบรรจง)
   วันที่ ....
4. ลายมือชื่อ .... กรรมการ
   อ. / ผศ. / รศ. / ศ. .... (เขียนชื่อ-สกุลตัวบรรจง)
   วันที่ ....

[signature]
(รศ.ดร.สุวัฒน์ ...)
หัวหน้าภาควิชาระบาดวิทยา

ลงนาม [signature]
(ผศ.ดร.ลักขณา ...)
ประธานหลักสูตร
วันที่ 30 เมษายน 2556

หมายเหตุ
1. ให้ส่งแบบฟอร์ม บฑ.33 ไปยังบัณฑิตวิทยาลัย ภายใน 15 วันทำการ หลังจากวันสอบ
2. กรณีผลสอบเป็น "ผ่าน" ต้องส่งแบบฟอร์ม บฑ.1 พร้อมกับ แบบฟอร์ม บฑ.33 ไปยังบัณฑิตวิทยาลัยด้วย
3. กรณีมีจำนวนคณะกรรมการฯ มากกว่า 4 ท่าน สามารถใช้แบบฟอร์ม บฑ. 33 เพิ่มเติมได้

4 ธันวาคม 2551

Documentary Proof of Exemption
Ethical Review Committee for Human Research
Faculty of Public Health, Mahidol University

Protocol Title :	INCIDENCE AND RISK FACTORS OF EXTENDED-SPECTRUM BETA-LACTAMASE-PRODUCING *E.COLI* NOSOCOMIAL INFECTION FROM URINE CULTURE IN 2011 AMONG INPATIENTS AT TAKSIN HOSPITAL BANGKOK METROPOLITAN ADMINISTRATION
Protocol No. :	66/2556
Principal Investigator :	Mrs. Somying Tipmongkol
Affiliation :	Master of Science (Public Health) Program in Infectious Diseases and Epidemiology Faculty of Public Health, Mahidol University

This protocol complies with a "Research with Exemption" category

Date of Issue : 28 May 2013

The aforementioned project have been reviewed and approved according to the Standard Operating Procedures of Ethical Review Committee for Human Research, Faculty of Public Health, Mahidol University.

S. Nanthamongkolchai

(Assoc. Prof. Sutham Nanthamongkolchai)

Chairman of Ethical Review Committee for Human Research

420/1 Rajvithi Road, Bangkok, Thailand 10400
Tel. (662) 3548543-9 ext. 1127, 7404 Fax. (662) 6409854

เอกสารยืนยันการยกเว้นการรับรอง
โดยคณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์
คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

ชื่อโครงการ : อุบัติการณ์และปัจจัยเสี่ยงของการติดเชื้อ *E.coli* ที่สร้างเอนไซม์ ESBL ในโรงพยาบาลจากผลการเพาะเชื้อจากปัสสาวะของผู้ป่วยใน ปี 2554 โรงพยาบาลตากสิน สำนักการแพทย์ กรุงเทพมหานคร

รหัสโครงการ : 66/2556

ชื่อหัวหน้าโครงการ : นางสมหญิง ทิพย์มงคล

หน่วยงานที่สังกัด : หลักสูตร วิทยาศาสตรมหาบัณฑิต (สาธารณสุขศาสตร์)
สาขาวิชาโรคติดเชื้อและวิทยาการระบาด
คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

โครงการวิจัยนี้เป็นโครงการวิจัยที่เข้าข่ายยกเว้นการรับรอง (Research with Exemption)

วันที่ออกเอกสาร : 28 พฤษภาคม 2556

ขอรับรองว่าโครงการดังกล่าวข้างต้นได้ผ่านการพิจารณาเห็นชอบตามมาตรฐานการดำเนินการของคณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์ คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

ลงนาม .....
(รองศาสตราจารย์สุธรรม นันทมงคลชัย)
ประธานคณะกรรมการพิจารณาจริยธรรมการวิจัยในมนุษย์

420/1 ถนนราชวิถี กรุงเทพมหานคร 10400
โทร 0-2354-8543-9 ต่อ 1127, 7404 โทรสาร 0-2640-9854

สมาคมศิษย์เก่าบัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล

ทุนการศึกษา ปี ๒๕๕๖

ประเภททุนอุดหนุนวิทยานิพนธ์บางส่วน

มอบให้แก่

นางสมหญิง ทิพย์มงคล

ให้ไว้ ณ วันที่ ๒๔ เดือนกรกฎาคม พ.ศ. ๒๕๕๖

ขอให้มีความสุข ความสำเร็จ

(ผู้ช่วยศาสตราจารย์สมศรี ดาวฉาย)
เลขาธิการ

(รองศาสตราจารย์ นายแพทย์มันตรี จุลสมัย)
นายกสมาคม

(รองศาสตราจารย์ผาสุวรรณ สนิทวงศ์ ณ อยุธยา)
ประธานพิจารณาทุนการศึกษา

Data collection form

ID…….……

Part 1: General characteristics; gender, age, department admitted, result of urine culture, admission date, day of culture and principle diagnosis.

1.1 Gender ☐ Male ☐ Female

1.2 Age…….....Years

1.3 Department admitted

☐ Medical ward ☐ Surgical ward ☐ Ob-gyn ward

☐ Intensive care unit

1.4 Result of urine culture

☐ *E.coli* ☐ ESBL- producing *E.coli* ☐ Other organism

☐ No growth

1.5 Principle diagnosis

☐ Hypertension ☐ DM ☐ Renal disease ☐ Malignant

☐ Heart disease ☐ UT ☐ Sepsis ☐ Other diagnosis

1.6 Admission date……..……..……

1.7 Day of culture…….……

1.8 Principle diagnosis…….……

Part 2: Risk factors

2.1 Prior antibiotics used within last year

☐ Yes ☐ No

2.2 Previous hospitalization

☐ Yes ☐ No

2.3 ICU stay during current admission

☐ Yes ☐ No

2.4 Urine catheter used within 30 days

☐ Yes ☐ No

2.5 Antibiotic used in this admission

☐ Cephalosporin group ☐ Other antibiotics

☐ No used antibiotic

2.6 Recurrent urinary tract infections

☐ Yes ☐ No

2.7 Invasive urine catheter

☐ Yes ☐ No

2.8 Co-morbidity

☐ Yes ☐ No

2.9 Diabetic mellitus

☐ Yes ☐ No

2.10 Hypertension

☐ Yes ☐ No

2.11 Renal disease

☐ Yes ☐ No

2.12 Malignant disease

☐ Yes ☐ No

2.13 Heart disease

☐ Yes ☐ No

2.14 Septicemia

☐ Yes ☐ No

Part 3: Results of infection from antimicrobial susceptibility of ESBL- producing *E.coli* from Taksin hospital laboratory reports (2011).

BIOGRAPHY

NAME	Mrs. Somying Tipmongkol
DATE OF BIRTH	1 November 1966
PLACE OF BIRTH	Prachuap Khiri Khan, Thailand
INSTITUTIONS ATTENDED	Kuakarun College of Nursing, 1984-1988 Diploma in nursing Science (Equivalent to Bachelor in Nursing) Kasetsart university, 2004-2006 Master of Science (Health Education) Mahidol University, 2009 Diploma in program of nursing specialty in infection control nursing Mahidol University, 2011-2015: Master of Science (Public Health) Major in infectious Diseases and Epidemiology
RESEARCH GRANTS	Partially founded by Mahidol University Alumni Association under the Royal Patronage of His Majesty the King academic year 2013
HOME ADDRESS	99/117 Baan Thunyapirom Rungsit –Nakhornnayok Rd., Bungsanun , Thunyaburi district, Pratumthani, Thailand Tel. 08 1811 3172 E-mail : somyingae@yahoo.com
OFFICE & POSITION	**Office:** Infection Control Department, Taksin Hospital, Bangkok Metropolitan Administration, Bangkok, Thailand **Position:** Infection Control Nurse