International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.12 No.02, pp 64-69, 2019

Risk Factors for Infection Caused by Extended-Spectrum Beta-Lactamase-Producing *Klebsiella pneumoniae* and *Escherichia coli* in Hospitalized Patients at Haji Adam Malik Hospital, Medan

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Abstract : It is important to recognize risk factors for infection caused by ESBL-producing *K.pneumoniae* and *E.coli*to describe effective strategy dealing with this infection. The aim of this research to identify risk factors associated with ESBL-producing*K.pneumoniae* and *E.coli* infection.A case control study was performed. Patient with ESBL-producing *K. pneumoniae* and *E. coli*(cases group) were compares to those with non-ESBL-producing *K. pneumoniae* and *E. coli*(control group). Risk factors analyzed included length of hospital stay before culture, prior hospital stay, type of hospital admission ward, recent surgery, invasive procedure and previous therapy with third generation cephalosporin.Sixty patients withESBL-producing *K. pneumoniae* and *E. coli*infection (cases group) were compares tosixty patients with non-ESBL-producing *K. pneumoniae* and *E. coli*(control group). By bivariate analysis risk factors length of hospital stay before culture, recent surgery, invasive procedure, and previous therapy with third generation cephalosporin to be associated with ESBL producing *K.pneumoniae* and *E.coli*. In multivariate logistic regression analysis, length of hospital stay before culture, recent surgery and previous therapy with third generation cephalosporin were remain significantly associated with ESBL producing *K pneumoniae* and *E.coli.*
Key words : *K. pneumonia, E. coli*, ESBL, risk factors.

Introduction

Extended spectrum beta lactamase (ESBL) is β-lactamase enzyme capable of showing bacterial resistance to penicillin, first, second and third generation cephalosporins and aztreonam (except cefamycin and carbapenem) by hydrolyzing these antibiotics and can be inhibited by inhibitors such as clavulanic acid[1,2].Since the first time ESBL was identified in 1983, microorganisms that produce ESBL are mainly found in Enterobacteriaceae especially *K. pneumoniae* and *E. coli*[3,4].

The surveillance results in 3 major cities (Surabaya, Semarang and Malang) during January-April 2010 showed the highest ESBL producers were K. *pneumoniae* (47.3%) and *E. coli* (42.7%).The isolation of ESBL

DOI= http://dx.doi.org/10.20902/IJCTR.2019.120209

found in the cities of Surabaya and Malang mainly came from urine specimens, pus, blood and sputum[3].Data from the Clinical Microbiology Installation of Adam Malik Hospital Medan in July - December 2012 showed the prevalence of ESBL *for E. coli* was 58.6% and for *K. pneumoniae* 69.7%.

Patients who have a high risk of being infected with ESBL-producing organisms are seriously ill patients who have stayed in the hospital for a long time, especially in Intensive Care Units and use invasive medical devices for long time (urine catheter, endotracheal tube, central vein, nasogastric tube, arterial line, patients with total parenteral nutrition, post-surgery, hemodialysis, and poor nutritional status). The use of third generation cephalosporins and aztreonam is also thought to be the main cause of mutations of ESBL[5,6,7,8,9].

Late detection of infection by bacteria that produces this ESBL and improper management will extend the length of stay and increase the burden of care costs as well as impact on mortality rates[9,10].Early identification of risk factors for ESBL infection needs to be done to find effective strategies to limit this infection[11]. Early identification of risk factors will also make empirical therapy be carried out immediately so that it will reduce morbidity and mortality[12,13].

Bacterial resistance to certain antibiotics will limit the choice of antibiotics that can be used in the incidence of infectious diseases while the choice of new antibiotics is limited[1,6,14]. One of the steps that need to be taken to anticipate bacterial resistance is prevention of bacterial resistance by knowing the risk factors [9,14,15]. The researcher considered it is necessary to conduct research on the risk factors associated with ESBL-producing *K. pneumoniae* and *E. coli* infections in Medan. The factors that will be examined are length of hospital stay before culture, recent hospital stay, type of hospital admission ward, recent surgery, invasive procedure and previous therapy with third generation cephalosporin.

Experimental

The research was conducted with anunmatched case control studyat Haji Adam Malik Hospital, Medan, North Sumatra, from March 2014 to June 2014.The population of this study was hospitalized patients at Haji Adam Malik Hospital.The samples were population that met the inclusion and exclusion criteria.

The inclusion criteria were hospitalized patients of Haji Adam Malik Hospital with ages 18-60 years and the culture results positive for *K. pneumoniae* and *E. coli*. Exclusion criteria were incomplete data, the duplication of bacterial isolates and Multi Drugs Resistant Organisms other than ESBL.

Case samples were patients with culture results for ESBL-producing bacteria *K. pneumoniae* and *E. coli*. The control samples were patients with culture results for non-ESBL-producing bacteria *K. pneumoniae* and *E. coli*. Case and control samples were taken by using a consecutive non repeated sampling. Everyhospitalized patient inHaji Adam Malik Hospital with the culture results of *K. pneumoniae* and *E. coli* bacteria that fulfilled the study inclusion criteria will be included as research samples until the required number of samples is fulfilled[16].

From the calculation of the number of samples for the 6 independent variables to be examined, the minimum number of samples taken was 58 samples for the case group and the control group, respectively. So that the total number of minimum samples needed for this study is 116.

The study started from the Clinical Microbiology Installation of Haji Adam Malik Hospital. All clinical specimens were processed and isolated using standard microbiological methods. Identification of ESBL and non-ESBL producing *K. pneumoniae* and *E. coli*was determined by automated Vitek 2 system (bioMérieux).

The clinical specimens were found with the growth of *K. pneumoniae* and *E. coli* bacteria, the patient who was the origin of the specimen would be visited on his ward.

The patient's identity, ward type of hospitalization (classified as categorical variables in two categories, namely ICU and non-ICU), specimen origin, length of stay before culture, history of hospitalization in the last 12 months, surgical history 30 days before, invasive procedure 72 hours before and history of third generation cephalosporin antibiotic therapy 30 days before were recorded using aquestionnaire.

Bivariate analysis was carried out to see whether there was a relationship between each independent variable with the ESBL-producing *K. pneumoniae* and *E. coli* infections. Bivariate analysis for categorical

variables was done by Chi Square test. For numerical variables bivariate analysis was performed with Mann-Whitney test to see a significant difference in mean length of stay before culture between positive ESBL group and negative ESBL group.

If a p value of <0.25 is obtained, the variable can be included in the multivariate analysis. In this study the multivariate analysis used was logistic regression analysis. To determine the significance of the results of statistical calculations used p value <0.05.

Result

During the study at Haji Adam Malik Hospital Medan, 120 samples of *K. pneumoniae* and *E. coli* from hospitalized patients were collected. From this samples, 60 patients from whom ESBL-producing *K. pneumoniae* and *E. coli*ESBLwere detected (cases) and 60 patients from whom non-ESBL-producing *K.pneumoniae* and *E.coli*were detected (controls).

In this study, the mean age was 43.4 ± 12.6 years in ESBL-producing *K. pneumoniae* and *E. coli*ESBL group and 45.3 ± 11.2 years in non-ESBL-producing*K.pneumoniae* and*E.coli*group. From ESBL-producing *K. pneumoniae* and *E. coli*group, male were 46(76.67%) and female were 14(23.33%). From the non-ESBL-producing *K.pneumoniae* and *E.coli* group, male were 36(60%) and female were 24(40%).

The source of clinical specimens in this study were 33,3% from sputum, 31,7% from pus, 10% from urine, 7,5% from feces, 5% from wound swab, 3,3% from blood and 9,2% from other type of speciments. From ESBL-producing *K. pneumoniae* and *E. coli*group, 34(56,67%) were *K. pneumoniae* and 26(43,33%) were *E. coli*. From the non-ESBL-producing *K.pneumoniae* and *E.coli* group, 30(50%) were *K. pneumoniae* and 30(50%) were *E. coli*.

The risk factors found significantly associated with the ESBL-producing *K. pneumoniae* and *E. coli* infections in bivariate analysis were length of hospital stay before culture, invasive procedure, recent surgery, and previous therapy with third generation cephalosporin.ICU ward type and prior hospital stay were not associated with ESBL producing *K.pneumoniae* and *E.coli*.

Table1. Bivariate Analysis Results

Variables	ESBL positive (60)	ESBL negative (60)	p-value	OR(95% CI)
ICU ward type, n(%)	8 (13,33%)	4 (6,67%)	0,224	2,15 (0,54-10,30)
Length of stay before culture, days	8,12± 7,0 days	3,5± 3,5	(p<0,001)	1,22 (1,10-1,35)
Prior hospital stay, n(%)	13 (21,67%)	6 (10,0%)	0,080	2,49 (0,80-8,58)
Invasive procedure, n(%)	45 (75,0%)	18 (30,0%)	<0,001	7,00 (2,92,-16,99)
Recent surgery, n(%)	24 (40,0%)	5 (8,33%)	<0,001	7,33 (2,41-26,45)
Previous therapy with third generation cephalosporin, n(%)	59 (98,33%)	29 (48,33%)	<0,001	63,10 (9,26-2612)

Multivariate analysis was applied by a logistic regression model to identify the risk factors associated with the ESBL-producing *K. pneumoniae* and *E. coli* infections. Previous therapy with third generation cephalosporin, recent surgeryand length of hospital stay before culture remained as risk factors associated with the ESBL-producing *K. pneumoniae* and *E. coli* infections.

Table 2. Multivariate Analysis Results

Variables	p-value	OR	95%CI
Previous therapy with third generation cephalosporin	<0,001	79,60	7,60-834,13
Recent surgery	0,024	4,66	1,22-17,77
Length of hospital stay before culture	0,002	1,24	1,08-1,42

Discussion

Identification of risk factors associated to ESBL-producing *K. pneumoniae* and *E. coli* infections is important to carry out management and control of infections that occur in hospitals[17]. The risk factors examined in this study were type of hospital admission ward (ICU, non-ICU), length of hospital stay before culture, prior hospital stay, invasive procedure, recent surgery, and previous therapy with third generation cephalosporin.

Results of bivariate analysis found that there were significant differences in the length of stay before culture between ESBL-producing *K. pneumoniae* and *E. coli* infections with non-ESBL-producing *K. pneumoniae* and *E. coli* infections. Previous studies also found length of stay before culture was significantly different between ESBL-producing *K. pneumoniae* and *E. coli* with non-ESBL-producing *K. pneumoniae* and *E. coli* infections [7,11,14,18]. Patients with longer hospitalizations have more severe disease and have more comorbid conditions[19,20]. Patients with more severe disease conditions have altered immune responses that have a greater risk of infection especially with *K. pneumoniae* which is an opportunistic pathogen[11,19].

Invasive procedures was significant risk factor for ESBL-producing *K. pneumoniae* and *E. coli*infection by bivariate analysis.Previous studies stated that the using of invasive devices (urinary catheter, intravenous catheter, arterial catheter, central venous catheter, intubation and mechanical ventilation) was associated with ESBL-producing *K. pneumoniae* and *E. coli* infection[14,22]. Invasive procedure damages the mechanical barrier which facilitates direct transmission of pathogen which often begin following contact with colonized patients, medical staff or contaminated objects[14].

Bivariate analysis in this study found a significant association between the recent surgery with ESBL-producing *K. pneumoniae* and *E. coli* infection. Previous studies also found a relationship between recent surgery with ESBL-producing *K. pneumoniae* and *E. coli* infection[14,17,24]. In surgery tissue damage occurs and the suppression of cellular immune response increasing the risk of infection in patients[25]. Risk factors for surgery are also related to epidemiological aspects such as the effectiveness of infection control carried out in a hospital[17].

In this study, bivariate analysis found a significant relationship between the use of third generation cephalosporins with ESBL-producing *K. pneumoniae* and *E. coli* infection. Previous studies also finding a relationship between the use of third generation cephalosporins with ESBL-producing *K. pneumoniae* and *E. coli* infection[7,14,17,21,24]. Third generation cephalosporin antibiotics are widely used in many hospitals. This antibiotic causes selective pressure so that ESBL-producing *K. pneumoniae* and *E. coli* emerge[7,19,21,23]. The use of this antibiotics will also eliminate or reduce the number of normal flora so that it will increase the susceptibility of individuals to get new strains that are resistant[19,26].

Type of ward (ICU ward type) and prior hospital stay were not associated with ESBL-producing *K.pneumoniae* and *E.coli* infection. Previous study also found no significant association between type of ward (ICU ward type) with ESBL producing *K.pneumoniae* and *E.coli* infection[11]. While other studies stated ESBL-producing *K.pneumoniae* and *E.coli* infection more commonly found in ICU[14,15]. ICU patients are generally at high risk, in a severe clinical state, have a high frequency of invasive procedures and large antibiotic pressure so that infection control is difficult to implement[14,15,19]. The findings of research vary from one study to another are related to the practice of prescribing local antibiotics and local infection control[19]. Previous study also found no association between prior hospitalization with ESBL producing *K.pneumoniae* and *E.coli* infection[17]. Whereas other study found a significant association between prior hospitalization with ESBL producing *K.pneumoniae* and *E.coli* infection[9,15,19]. More frequent contact with health facilities increases the likelihood of getting infection with ESBL producing *K.pneumoniae* and *E.coli*[23].

Multivariate logistic regression analysis in this study identified variables that still remainedas risk factors for ESBL producing *K.pneumoniae* and *E.coli* infection were the use of third generation cephalosporin, recent surgery and length of stay before culture .

In this study the OR for third generation cephalosporin use was 79,60 (95% CI 7,60-834,13). Previous research and multivariate analysis of third generation cephalosporin use for ESBL producing *K.pneumoniae* and *E.coli* infection also found a significant relationship (OR 6,0-28,4 ; 95% CI 2,59-215,8)[7,24,27].

Recent surgery in this study was still significant risk factor with OR 4,66 (95% CI 1,22-17,77). Previous study with multivariate analysis also found relationship between recent surgery andESBL producing *K.pneumoniae* and *E.coli* infection(OR 10.35 ; 95% CI 1,9-55,6)[17].

Length of stay before culture in multivariate analysiswas also associated with ESBL producing *K.pneumoniae* and *E.coli* infection (OR 1,24 ; 95% CI 1,08-1,42). Previous research with multivariate analysis also found an association between length of stay before culture with ESBL producing *K.pneumoniae* and *E.coli* infection (OR 1,06-1,10; 95% CI 1,02-1,16)[19,20].

These risk factors that have been identified are an important starting point for the management and control of ESBL producing *K.pneumoniae* and *E.coli* infection. Early identification by knowing risk factors can improve empirical therapy and thus reduce morbidity and mortality rates.

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