Research Article

# Patients Infected by Extended-Spectrum Beta-Lactamase Producing *Klebsiella pneumoniae*: Risk Factors and Outcomes

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***Abstract***

*Infections due to resistant bacteria including Extended-Spectrum Beta-Lactamase (ESBL) producing Klebsiella pneumoniae becomes the major health problem worldwide. The aim of this study is to understand the prevalence of ESBL producing K. pneumoniae in Intensive Care Unit (ICU) dr. Cipto Mangunkusumo National Hospital (CMNH) and also to understand the risk factors related to these bacteria and its correlation with patients' outcomes. This retrospective study using the sample from clinical isolates of ICU's patients in CMNH who were treated in 2011 and known to have an infection with the K. pneumoniae based on microbiological examination. Phenotypic confirmation for ESBL conducted using double disk synergy test (DDST) and patient's history of illness was traced through the medical record. From 35 patients infected by K. pneumoniae, 25 isolates were ESBL positive. Central venous catheter (CVC) utilization is found to be a probable risk factor in getting an infection by such bacteria. Infection by ESBL producing K. pneumoniae could prolong ICU stays more than 20 days.*
***Keywords:*** *K. pneumoniae, ESBL, risk factors, outcomes.*

# Infeksi oleh *Klebsiella pneumoniae* penghasil *Extended-Spectrum Beta-Lactamase* (ESBL): Faktor Risiko dan Luaran Klinis

***Abstrak***

*Infeksi yang disebabkan oleh bakteri resisten termasuk Klebsiella pneumoniae penghasil Extended-Spectrum Beta-Lactamase (ESBL) saat ini menjadi masalah kesehatan utama di seluruh dunia. Tujuan penelitian ini adalah untuk mengetahui prevalensi K. pneumoniae penghasil ESBL di Intensive Care Unit (ICU) Rumah Sakit Umum Pusat Nasional dr. Cipto Mangunkusumo (RSUPNCM) serta mengetahui faktor risiko terkait infeksi oleh bakteri tersebut dan hubungannya dengan luaran klinis pasien. Penelitian ini merupakan suatu studi restrospektif pada isolat pasien ICU RSUPNCM yang dirawat pada tahun 2011 dan diketahui mengalami infeksi oleh bakteri K. pneumoniae berdasarkan pemeriksaan mikrobiologi. Uji konfirmasi fenotip ESBL dilakukan dengan teknik DDST dan data pasien ditelusuri pada rekam medik. Dari 35 pasien yang terinfeksi oleh K. pneumoniae, 25 isolat merupakan penghasil ESBL. Penggunaan kateter vena sentral dapat menjadi faktor risiko terinfeksi oleh K. pneumoniae penghasil ESBL dan infeksi oleh bakteri tersebut dapat memperpanjang lama rawat pasien di ICU hingga lebih dari 20 hari.*
***Kata kunci:*** *K. Pneumoniae, ESBL, faktor risiko, luaran klinis.*

## Introduction

Among the group of gram-negative rods, especially the *Enterobacteriaceae* family, *Klebseilla pneumoniae* is a bacteria that is widely reported as multidrug-resistant (MDR) that cause infections in intensive care unit (ICU)'s patients.[1-4] It cause a wide spectrum of infections, such as urinary tract infection (UTI), pneumonia, intra-abdominal infection, bloodstream infection (BSI), meningitis, and pyogenic liver abscess.[5] *K. pneumoniae* utilizes a variety of virulence factors, especially capsule polysaccharides, adhesins, and determinants for iron acquisition, which are used for survival and immune evasion during infection. Typically, *K. pneumoniae* is an opportunistic pathogen, which mostly affects those with weakened immune systems and tends to cause hospital-acquired (HA) infections.[6] The resistance mechanism in *K. pneumoniae* is mainly by producing the beta-lactamase enzyme,[4,7] The early detection of the presence of these resistant strains at the phenotypic level would help to select appropriate antimicrobial treatment in order to decrease the morbidity and mortality.[9] In addition, a phenotypic confirmatory test is also beneficial to the interests of epidemiology and infection control to minimize the dissemination.

Infection by ESBL producing *K. pneumoniae* often limit therapeutic options and is associated with treatment failures or bad clinical outcomes.[10,11] Some of the risk factors associated with nosocomial infection by ESBL producing *K. pneumoniae*, namely the previous use of antibiotics; use of invasive devices such as urinary catheters (indwelling), tracheal tube, and CVC; age >65 years; hospital care in the last 3 months; and the presence of comorbidities such as respiratory disease, cardiovascular disease, hypertension, diabetes mellitus, kidney disease, liver disease, malignancy, and patients in corticosteroids therapy.[12-17] Infection by this organism is associated with treatment failure resulting in longer hospitalization, an increase of cost treatment, and increase patient's mortality.[10,13]

The objective of the study is to identify ESBL producing *K. pneumoniae*, analyze risk factors and assess the clinical outcomes of patients infected by the bacteria.

## Methods

This is a retrospective study with the samples including all stock isolates from ICU's patients in dr. Cipto Mangunkusumo National Hospital (CMNH) during 2011 with the identification results is *K. pneumoniae* (35 isolates) based on microbiology examination. All the data of patient were obtained from the hospital medical record. Before processing, stock isolates were kept on -80$^{o}$C and re-identified using conventional biochemical test. We used *K. pneumoniae* ATCC 700603 as the control strain. This is an advanced development of the study published by Saharman.[18]

We used the DDST to confirm ESBL producing (Figure 1), ESBL phenotypic confirmatory test performed on isolates had decreased susceptibility to cephalosporins and/or aztreonam, as recommended by the Clinical and Laboratory Standard Institute (CLSI) 2011 (inhibition zone diameter of cefpodoxime <17 mm, ceftazidime <22 mm, ceftriaxone <25 mm, cefotaxime <27 mm, and aztreonam <27 mm).[19] In CLSI recommendation, disc used for ESBL confirmatory test are ceftazidime, ceftazidime-clavulanic acid, cefotaxime, and cefotaxime-clavulanic acid. However, because ceftazidime-clavulanic acid and cefotaxime-clavulanic acid are not available in Indonesia, we used amoxicillin-clavulanic acid disc 30 mg based on the publication of Drieux et al.[20] In this study, we also used control strain, namely *K. pneumoniae* ATCC 700603 as a positive control and *E. coli* ATCC 25922 as a negative control.

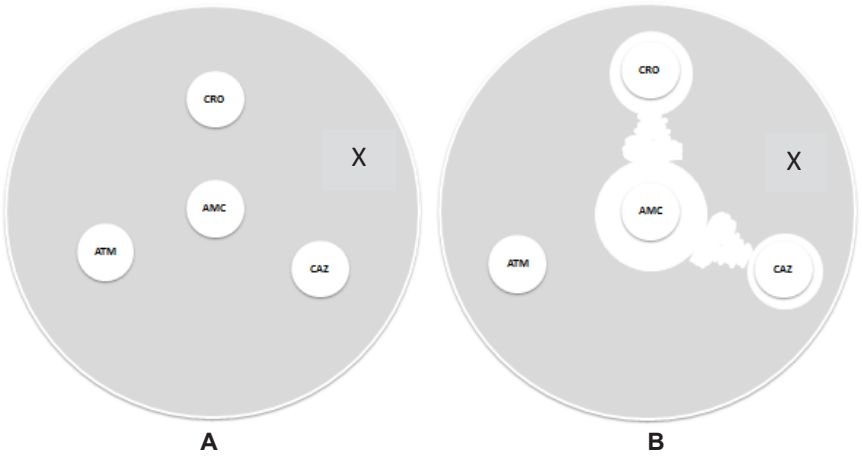


**Figure 1. (A) ESBL Confirmatory Test with DDST. (B) Positive ESBL with DDST**

X: bacterial suspension 0,5 McF inoculated in Mueller Hinton Agar (MHA) plat; AMC: amoxicillin-clavulanic acid disc; CRO: ceftriaxone disc; ATM: aztreonam disc; CAZ: ceftazidime disc

Analysis data was performed using SPSS version 16.0 to determine the relationship between various variables of risk factors with the incidence of infection by ESBL producing *K. pneumoniae*, and also to determine whether the infection could influence patients' length of stay (LOS) in ICU and clinical outcomes. For LOS variable in the ICU, we used time limit of >14 days and ≤14 days based on the previous study.[16] Clinical outcome variable only differentiated either patients clinically improved during treatment in the ICU or the patient died. This study has passed the Faculty of Medicine, Universitas Indonesia/CMNH Ethics Committee evaluation (No. 318/PT02.FK/ETIK/2012).

## Results

Out of 35 isolates, 33 have decreased susceptibility to cephalosporins and/or aztreonam and using DDST we found 25 isolates were ESBL producing. After that, the patient's data were obtained from the medical record to find the risk factors and outcomes. Male and female patients were almost equal and most of them used one or more invasive devices. Detail of the patients' characteristic is summarized in Table 1.

There was no correlation between risk factors observed in this study and the incidence of ESBL producing *K. pneumoniae* infection except the use of CVC. In addition, ESBL producing *K. pneumoniae* infection did not correlate with the patient's outcome. The results of the analysis are summarized in Table 2.

**Table 1. Patient's Characteristics**

| Characteristics | n |
|---|---|
| Gender | |
| Male | 19 |
| Female | 16 |
| Diagnosis category | |
| Surgery | 25 |
| Medical | 10 |
| Specimens type | |
| Sputum | 24 |
| Non-sputum | 11 |
| Age | |
| >65 years | 7 |
| ≤65 years | 28 |
| Ward origin | |
| Ward | 23 |
| Emergency department | 12 |
| Invasive devices | |
| Urine catheter | 35 |
| CVC | 29 |
| Mechanical ventilation | 34 |
| Antibiotics history | |
| 3rd/4th generation Cephalosporins | 17 |
| Aminoglycosides | 14 |
| Fluoroquinolones | 6 |
| Carbapenems | 17 |
| Comorbidity | |
| With comorbid | 13 |
| Without comorbid | 22 |

**Table 2. Risk Factors and Patient's Outcomes Correlation with ESBL Producing *K. pneumoniae* Infection**

| Risk Factors and Outcomes | p-value | OR |
|---|---|---|
| *Risk Factors* | | |
| Diagnosis category | 0.686 | - |
| Age (>65 years) | 0.644 | - |
| Ward origin | 0.059 | - |
| Invasive devices | | |
| CVC | **0.043** | **7.6667** |
| Mechanical ventilation | 0.286 | **-** |
| Antibiotics history | | |
| 3rd and/or 4th generation cephalosporins | 0.711 | - |
| Aminoglycosides | 0.704 | - |
| Fluoroquinolones | 0.152 | - |
| Carbapenems | 0.771 | - |
| Comorbidity | 0.709 | - |
| *Outcomes* | | |
| LOS | 0.508 | |
| Clinical Improvement | 0.709 | |

## Discussion

The number of ESBL producing *K. pneumoniae* in this study is quite high compared to other countries such as Taiwan and Korea, whereas the prevalence was around 26% in 2005,and 59% in Thailand in 2008.[13] The SENTRY Asia-Pacific Surveillance Program conducted in 1998-2002 results revealed the highest prevalence was in Jordan and Saudi Arabia (>60%).[1] Meanwhile, other studies in different regions/provinces in Indonesia showed lower prevalence i.e. 24.7% in Surabaya, East Java[21] and 13.7-25% in Bandung, West Java.[22] Our result is quite similar to a recent survey in India with ESBL producing *Enterobacteriaceae* percentage are 70-90%.[3] This indicates that the bacteria have already spread in Indonesia, considering that CMNH is a national referral hospital. Knowing the risk factors and outcomes due to infections by these bacteria are very beneficial to establish the infection control measures in the hospital.

The majority of patients admitted to the ICU were post-surgical indications. Most sputum specimens showed a diagnosis of infection in patients of pneumonia. This is consistent with the literature which states that *K. pneumoniae* is the most gram-negative bacteria that cause respiratory tract infections (pneumonia) in addition to BSI, UTI, intra-abdominal infection, and liver abscess.[5]

Age of patients with infection by *K. pneumoniae* in ICU of CMNH varies during 2011, with a minimum age of 7 years and a maximum of 86 years, with a median of 52 years. For further analysis, age was divided into 2 categories i.e. >65 years and ≤65 years, because according to the literature age >65 years have a greater risk factor for infection by ESBL producing *K. pneumoniae*.[16]

In addition to the risk factor of age, the presence of comorbidities is also known to be a risk factor for infection by ESBL producing *K. pneumoniae*.[5,12,14,16] In this study 13 patients had comorbidities, including hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, cerebrovascular disease, intracranial tumors, chronic kidney disease, kidney tumor, hepatitis B, HIV infection, and a history of cardiac arrest.

We also differentiated the origin of the patient wards before ICU admission (wards and the emergency department/ED), as well as the history of the use of antibiotics (3rd and/or 4th generation cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems).

Based on Table 2, it can be concluded that the diagnosis, age >65 years, ward origin, a history of antibiotic, and the presence of comorbid did not reach statistical significance as risk factors for infection of ESBL producing *K. pneumoniae*. The use of invasive devices, i.e. CVC is statistically significant as a risk factor with p-value 0.043 and OR 7.667. This suggests a positive relationship, the patients using CVC are 7 times more likely will get ESBL producing *K. pneumoniae* infection than those who don't.

Other studies with small sample size as Ikeda et al[12] with a sample size of 28 and Cordery et al[17] the number of samples 55, have no relationship for various risk factors, including age, ward origin, previous hospitalization, comorbidities, use of invasive devices, and prior use of antibiotics.[12,17] However, other studies with a large number of samples conducted by Saonuam et al[13] (576 samples), the risk factors associated with the incidence of infection by ESBL producing *E. coli* and *K. pneumonia* are the use of CVC and a history of antibiotic use (3rd generation cephalosporin and fluoroquinolones). As for age, ward origin, and the use of carbapenem have no relationship.[13]

Differences in research outcomes in various countries even with large sample size mentioned before, suggests that risk factors for infection by ESBL producing bacteria are strongly influenced by local conditions. Calvalhaes et al[2] mentioned

that there are currently three key challenges in overcoming *K. pneumoniae* MDR, namely 1. medical challenges, such as the unavailability of a rapid detection method, patients do not receive adequate treatment, and infection control measures are not effective; 2. the challenges of science, such as antibiotics and the development of new methods for detection; 3. community challenges, such as environmental or food contamination.[2] Some other studies suggested that in order to get better analysis results, a study is better conducted with the case-control study design and selection criteria of the pairs (matching criteria) for each group of cases and control set specifically to avoid bias.[13-15] Based on Table 2, there is no relationship for the LOS patients in ICU with infection by ESBL producing *K. pneumoniae*. The length of hospitalization in patients with infection by ESBL producing in this study was 22 days, whereas the non-ESBL producing was 11 days. Although not statistically significant, hospitalization 11 days hospitalization differences between the 2 groups in clinical practice course may affect patient morbidity, including the extent of treatment cost and loss of patient's income during the treatment in the hospital. For comparison, Carvalhaes et al[2] points out that the average length of hospitalization of patients with infection by MDR gram-negative bacteria is longer than infection by a susceptible strain, which is 29 days vs 13 days (difference of 14 days), and the difference was statistically significant ($p<0.0001$).[2] The p-value is associated with the sample size, but in fact, in clinical practice, there is no direct relationship between the value of p with large effect. That is why effect size (ES) is often used as a basis for assessing the clinical significance.[23] In this study, we calculated the ES by comparing infection by ESBL producing *K. pneumoniae* and non-ESBL producing LOS in ICU. When the mean (M) and standard deviations (SD) were included in the web-based ES calculator, we found d=0.4. According to Cohen's interpretation, ES value of d=0.4 in this study means that infection by ESBL producing *K. pneumoniae* have a small to moderate effect in affecting LOS in ICU patients.[23]Infection by ESBL producing *K. pneumonia* was not statistically significant for patient's outcome (dead or clinically improved) with p=0.709. We also assessed ES and found d=0,2, which means that infection by ESBL producing *K. pneumoniae* has a small effect on patient's outcome in ICU. However, in a clinical context, the death of one patient will be very valuable, as quoted by Durlak[23]calculation, and interpretation of effect sizes (ESs that the ES is hanging with the situation, a small effect on the one outcome can be more important than the effect of the other outcome. Other study mentioned that to evaluate the patient's outcome, it is recommended to use the score of "The Sequential Organ Failure Assessment" (SOFA) and "The Acute Physiology and Chronic Health Evaluation" (APACHE),[24] so the value is more measurable and this could be an improvement for further research.

This study has a few limitations to be considered. Two groups compared (ESBL producing and non-ESBL producing) were unmatched, which may lead to statistical bias. Given that the study is retrospective, some data were incomplete and could affect the analysis. Better analysis results could be obtained by designing a case-control study, which is conducted by selecting the criteria for each case and control groups specifically to avoid bias. A prospective study would help the researcher to obtain more complete and accurate data. In addition, results of this study could be a basis to make guidelines, monitoring, and reporting system of the incidence of infection by MDR gram-negative bacteria, especially ESBL producing *K. Pneumoniae,* as well as to establish the standard of empirical therapy for patients admitted to the ICU. We can also implement contact precautions for patients with this bacterial infection to prevent transmission to other patients.

## Conclusion

This study revealed that 25 isolates out of 35 isolates of K. pneumoniae were ESBL producing and strongly associated with the use of CVC. Although not statistically significant, infection by this bacteria can prolong hospital care of the patient that reaches more than 20 days.

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